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NUTRITION REVIEWS

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Erratum

Vol. 7, No. 1, page 7, 1st article, column 1, line 22 (*ca* 60 per cent) *should read* (*ca* 85 to 90 per cent)

NUTRITION REVIEWS

VOL. 7 MARCH, 1949 No. 3

THE ARMY'S MEDICAL NUTRITION LABORATORY

The U. S. Army Medical Department has certain responsibilities regarding nutrition of the troops, and has centered much of its nutrition research in the Medical Nutrition Laboratory. As it now exists, this laboratory had its start in 1917 to 1918. In the Nutrition Division of the Office of The Surgeon General were scientists such as John Murlin, Philip Shaffer, Anton J. Carlson, and Paul Howe, and the results of World War I research in Army feeding were summarized in a series of papers in the *American Journal of Physiology* in 1921 to 1922. During the interwar period, Medical Department research on Army nutrition decreased to a laboratory on paper, which started active work on a small scale early in World War II in Washington, D. C., under the immediate command of Major George H. Berryman, Sn.C. In 1944, plans were made to move the laboratory to Chicago so as to be near the big food industries and to be closely connected with the Quartermaster Subsistence Research and Development Laboratory. Administration of the Medical Nutrition Laboratory was radically altered in October, 1946. In both personnel and variety of activities the laboratory has expanded considerably since V.E. day.

Under Army regulations it has three missions. The first is to investigate the health of troops in all environments to make sure that they are well fed, as healthy and as fit as is compatible with local danger, disease, and environment. The second is to prevent and to treat disease and damage in so far as is possible by nutritional and metabolic means. The third is to be in a position to observe and make recommendations on the nutrition and health of civil populations under military control. Col. William S. Stone wrote an enlightening article in the *Bulletin of the U. S. Army Medical Department* (*January 1947*) outlining ten general areas of medical research which have always been important in war or which are bound to be important in the future. The program of the Medical Nutrition Laboratory is built around its three missions in view of the important areas of research outlined in that article, since nutritional and metabolic problems are significant in all fields of medicine. Present laboratory personnel have worked under all three of its missions. The health of troops in all environments has been studied in the desert (1942–1943), in the arctic and subarctic (1944, 1946, 1947), in the mountains (1944, 1946), in the Pacific (1945), and in India and Burma (1944–1945). Clinical investigation is being conducted now on liver disease, neurologic disorders, anemia in relation to chronic infection, and vitamin A metabolism in lung disease. During 1945 the laboratory made a thoroughgoing study of the clinical manifestations of experimental deficiency in the lesser-known members of the vitamin B-complex (including folic acid, biotin, and pantothenic acid). Studies on civilian populations were made by teams sent out to Holland before V.E. day and to Austria after V.E. day. Research has been continuous on the dietetic problems involved in preparation of special diets for Army hospital feeding, and similarly on animals as they relate to human problems.

The present staff numbers 68, about half military and half civil service. The laboratory headquarters handles both military and civil service administration. This bilateral type of activity works very well but does pose administrative problems more complicated than those commonly met in university laboratories. The research branches of the laboratory include: a Medical Dietetics Division; a Technical Research Division, with its three branches, animal, biochemical, and

microbiologic research; a Clinical Investigation Division; a Pathology Division; and a Radiobiology Division. Accessory departments furnish the usual facilities that a research laboratory needs including library, statistics, glass blowing, and other activities.

The Medical Dietetics Division has worked hard on the problem of devising palatable high protein diets without unduly increasing the bulk and caloric content of the diet. Their general philosophy has been to increase the protein content of all items of the diet so that the patient if he eats anything will receive a high protein diet. A recent study on high protein feeding in rheumatic fever has just been completed.

The Animal Research Branch is studying changes which occur in animals during rehabilitation after various kinds of malnutrition with particular emphasis on the effects of calories, salts, and low protein intakes. They are concerned primarily with any permanent changes which cannot be rectified during rehabilitation and are ultimately interested in determining the best diets for rehabilitation of starved human beings.

The Clinical Investigation Division, in a metabolic ward at the Univ rsity of Illinois and in two of the Army General Hospitals, is studying a considerable variety of case material. A long-term study of the relative merits of human albumin and various types of amino acid preparations as used in chronic and acute liver disease is nearing completion. The anemia of chronic infection has been attacked by a combined bacteriologic and hematologic approach. Significant findings to date indicate that the degree of anemia in patients with osteomyelitis is determined not by the total bacterial count in the wound but by the number of different species of bacteria present. Therapeutic trials of various hematopoietic agents are now in progress. This division has published several papers on the neurologic disorders produced in dogs by wheat flour treated with the bleaching agent, agene.

The Pathology Division has embarked on a study of the diseases of connective tissue in their relation to metabolic and nutritional factors with special emphasis on ascorbic acid and the adrenocortical hormones.

The Radiobiology Division is engaged in a study of tissue damage in general. As has been emphasized repeatedly in the press, the atomic bomb injures man in many ways including blast, thermal damage, thermal radiation, ultraviolet radiation, x-radiation, as well as from absorption of radioactive particles. To date the only therapeutic measures suggested other than surgical have been nutritional in nature.

On occasion it is necessary for the laboratory staff to conduct investigations in the field. At these periods much of the laboratory may be converted to a field research laboratory. A recent study of this type involved the transportation of soldiers into the frozen north.

The whole aim of the Medical Nutrition Laboratory is to assist the Medical Department of the Army in assuring that the troops are healthy and well fed. Medically speaking, soldiers are no different from civilians and therefore results of the laboratory's work are directly applicable to many problems of ordinary civilian life.

ROBERT E. JOHNSON
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DIETARY CONSTITUENTS AS ALLERGENS

It is commonly conceded that constituents of the diet may be the cause of various types of allergic disease. In clinical practice, cases of dermatitis, rhinitis, hemorrhage into the skin, colitis, and asthma apparently due to food are observed. However, it is often difficult to evaluate the relative role of various dietary components as allergens.

Results of skin tests with extracts of foods may be misleading and afford little information of value in planning a program of therapy (L. W. Hill, *J. Allergy* **13,** *366 (1942)*; S. F. Hampton, *Ibid.* **12,** *579 (1941)*).

A fact of fundamental importance in the diagnosis and treatment of allergic disease is that when offending substances are removed from the environment of the patient, clinical manifestations of sensitivity ameliorate or disappear, and exacerbate or reappear when the allergens are again introduced into the patient's environment. Advantage is taken of this fact in the use of elimination diets in food allergy. In this procedure specific foods or groups of foods are eliminated from the diet and the individual carefully observed for remission of symptoms and signs of sensitivity. By this means offending foods are frequently designated and treatment includes continued exclusion of those foods from the diet of the patient. In more severe forms of food allergy there may be a number of food factors responsible and it may be necessary to continue the use of elimination diets for prolonged periods before the causative agents are ascertained. Often this is to the detriment of the general health and state of nutrition of individuals affected.

W. H. Olmsted, C. G. Harford, and S. F. Hampton (*Arch. Int. Med.* **73,** *341 (1944)*) called attention to the advantages which may pertain in the use of diets free of natural foods. Protein hydrolysates and amino acid mixtures are demonstrated not to be antigenic. The inclusion of these in a purified diet makes it possible to sustain approximately normal nutrition while determining the importance of the natural foods as allergens. A purified diet containing a casein hydrolysate, dextrose, an emulsion of corn or cottonseed oil, minerals, and a vitamin mixture and meeting basic nutritional requirements was given through a stomach tube to patients in whom it was considered likely that food substances were of etiologic importance in allergic disorders. Within a week of institution of such a dietary regimen it was usually found that manifestations of sensitivity would improve or abate if due to constituents of the diet. It was often possible by the addition of single foods to determine which were of etiologic significance.

A report of P. Rowe and J. M. Sheldon (*J. Lab. Clin. Med.* **33,** *1059 (1948)*) describes the use of a similar procedure in the study of 51 patients suffering from various diseases considered to be of allergic origin. Diets utilized were free of intact food proteins. Casein hydrolysates (Amigen or Protolysate) served as a nitrogen source. Sucrose, Dextri-maltose, starch, and dextrose were used as dietary carbohydrates. Olive oil was included in some of the diets. In addition, mineral salts and synthetic vitamins were provided. The diet was given orally in quantities considered sufficient to meet caloric needs.

Before the institution of this dietary regimen attempts were made to explore the possibility that symptoms arose from causes other than foods. An allergic history was taken and skin tests done. A four to six day period of adjustment in the hospital was allowed to evaluate the relation of the patient's home and work environment to his allergic state. Attempts were made to control dust in the hospital rooms. Respiratory infections were treated with chemotherapeutic or antibiotic agents. Symptomatic and collateral treatment was simplified or, when possible, eliminated so that effects of the diet might be more adequately evaluated.

A ten day period on the purified diet was usually sufficient to induce remissions of allergic disorders resulting from foods. Absence of ameliorative changes at the end of this period was considered an indication that food allergy probably was not important in etiology. The 51 patients included in the study had a variety of allergic disorders of severe degree and of daily occurrence. Twenty-six suffered from bronchial asthma and 7 from allergic dermatitis.

An analysis of results of this appraisal

demonstrated that in 15 patients symptoms cleared while the synthetic diet was taken and were reproduced by additions of specific foods to the experimental diet. The foods most frequently ascertained to function as allergens in these patients were milk, wheat, white potato, and beef. There was marked failure of correlation between the results of skin tests and the clinical response to withdrawal of natural foods. Skin sensitization occurred in but 27 per cent of instances of foods demonstrated to serve as allergens by the use of the synthetic diet.

Twenty-three patients after ten days on the experimental diet failed to demonstrate beneficial response. In these, therefore, the authors concluded that food allergies did not contribute to the patients' illness. In 13 others, results were equivocal and did not permit an adequate evaluation of food factors as offending substances.

There would seem to be definite advantages both to the patient and to the clinician in the use of a purified diet, relatively or wholly free of potentially allergic materials, in the diagnostic study of food allergy. However, it should be repeated that such a procedure should not be followed until adequate attempts have been made to rule out other forms of allergy such as those due to drugs, inhalants, and contact. Lack of palatability of this type of diet mitigates against its effectiveness as a procedure for general application. Rowe and Sheldon reserved its use for cases of most severe and intractable allergic disease. The quantities consumed by their patients did not permit maintenance of body weight. These limitations might conceivably be avoided by use of a stomach tube through which frequent feedings are given or by attempts to improve the palatability of the diet without addition of substances likely to serve as allergens.

URINARY EXCRETION OF AMINO ACIDS AFTER ADMINISTRATION OF PROTEIN HYDROLYSATES

A factor limiting the efficiency of utilization of protein hydrolysates administered intravenously is the extent of the loss of amino acids into the urine during and immediately after the infusions. Attention previously has been directed to the much larger wastage of the peptides than of the free amino acids of partial hydrolysates (*Nutrition Reviews* **6,** *53* (*1948*)). Information about the normal human excretion of amino acids has heretofore been limited.

Simultaneous reports by S. W. Hier (*Tr. N. Y. Acad. Sci.* **10,** *280* (*1948*)) and by R. D. Eckhardt, A. M. Cooper, W. W. Faloon, and C. S. Davidson (*Ibid.* **10,** *284* (*1948*)) have dealt with the urinary excretion of amino acids by human beings receiving intact or hydrolyzed proteins at various levels. In so far as the studies cover similar subjects the findings are in agreement. Hier, using microbiologic test methods on acid hydrolysates of urine (*see also* H. W. Woodson, S. W. Hier, J. D. Solomon, and O. Bergeim, *J. Biol. Chem.* **172,** *613* (*1948*)) found that 18 college students on their usual dietary regimen excreted a mean of 1.3 mg. of free aspartic acid per day, while the other amino acids were excreted in larger amounts, up to a mean of 188 mg. of histidine. Virtually all of the aspartic acid and glutamic acid was excreted in the combined form while histidine was entirely in the free state. When the total of the free and combined excretion was measured, the values ranged from 20 mg. per day of isoleucine to 351 mg. of glutamic acid. The other nine essential amino acids and four other nonessential amino acids were included in the study. A strict distinction is of course not obtained between free and combined amino acids by microbiologic assay, since in many instances combined amino acids are available to the test organism (H. N. Christensen and D. M.

Hegsted, *J. Biol. Chem.* **158,** *593 (1945)*). Statement of the analytical results for the various amino acids in terms which permit comparisons and calculations among them, for example, milligrams of alpha-amino nitrogen, seems desirable.

Eckhardt and his colleagues observed that when the normal daily diet, estimated to contain 105 g. of protein, was removed altogether, the hourly excretion of alpha-amino nitrogen (manometric ninhydrin method) dropped only from 6.6 to 4.3 mg. per hour. The loss induced by the ingestion of 105 g. of protein was calculated to represent only 0.4 per cent of the amino nitrogen ingested. The excretion of combined amino nitrogen released by acid hydrolysis was about four times as great as the free, whether the subjects were fasting, on normal diets, or on diets restricted in protein.

The excretion of amino acids, and more particularly of peptides, appeared to be much larger following intravenous infusions of partial hydrolysates of protein, although the amounts varied with the source of the protein. Consequent to four daily infusions of 75 g. of a partial casein—pancreas hydrolysate (Amigen)—one subject excreted 1.6 g. of nitrogen daily (representing 10 g. or more of protein) of which four-fifths was in combined form. The combined nitrogen excreted represented about 45 per cent of the peptide alpha-amino nitrogen injected, whereas less than 5 per cent of the free alpha-amino nitrogen was lost. H. N. Christensen and his collaborators (*Nutrition Reviews* **6,** *53 (1948)*) called attention to the large excretion of peptides following infusion of partial hydrolysates into human subjects. On the other hand, Christensen found that two partial hydrolysates of fibrin yielded only 10 to 28 per cent of their combined alpha-amino nitrogen in the urine. Since free amino acids are subjected to smaller urinary losses than peptides, Eckhardt concluded that completely hydrolyzed protein was probably superior to partially hydrolyzed protein for intravenous nutrition.

Retention of administered amino acids appeared to be relatively efficient even at high rates of infusion of a modified casein hydrolysate. Five hundred ml. of a 10 per cent solution were infused into 8 fasting subjects at three rates of infusion, namely in sixty, twenty, and ten minutes. The plasma alpha-amino nitrogen rose to 22.5 mg. per 100 ml. five minutes after the infusion, fell to 7.2 mg. one hour later, and was normal within four hours. The increased amino acid excretion represented 1.5 to 8.4 per cent of the various essential amino acids, except that losses of histidine and threonine were 14.4 and 17.8 per cent. At the slowest rate of infusion the losses of histidine, threonine, and tryptophan were 12.9, 14.1, and 5.7 per cent respectively; the maximum loss of any other amino acid studied was 3.5 per cent. The patterns of retention by the body of the ten essential amino acids thus differed from the patterns of administration; threonine, histidine, lysine, tryptophan, and phenylalanine were in relatively greater concentration in the urine than in the infusion mixture, whereas arginine, isoleucine and leucine, methionine, and valine were in smaller concentration. Arginine was retained to the highest degree with less than 1 per cent of the amount ingested appearing in the urine (Hier observed the greatest retention with methionine). No evidence was offered to explain the reason for these differences in patterns, although several possibilities were suggested. From the fact that each increase in infusion rate produced increases in excretion which more closely paralleled the composition of the infusion mixture, it would appear likely that differences in renal clearance may have been chiefly responsible for the difference in patterns.

The requirements for an individual amino acid when fed parenterally were found to exceed the oral requirements. Nitrogen balance was maintained on oral feeding of a hydrolysate containing minimal quantities of phenylalanine, but additional phenylalanine was needed to supplement this mix-

ture for parenteral feeding. In addition to the larger urinary losses, it seems likely, as pointed out by the authors, that the increased requirement may have been due to lack of sufficient carbohydrate to achieve maximum protein retention.

C. J. Smyth, S. Levey, and A. G. Lasichak (*J. Clin. Invest.* **27,** *412 (1948)*) compared the urinary excretion of both free and combined alpha-amino nitrogen following administration of three protein hydrolysate preparations. These included an enzymatic hydrolysate and two acid hydrolysates. The total amino acid loss was greatest following infusion of the enzymatic hydrolysate due largely to the excretion of combined amino acids. R. H. Silber, E. E. Howe, and C. C. Porter (*Tr. N. Y. Acad. Sci.* **10,** *277 (1948)*) studied the utilization of six hydrolysates in dogs. This report failed to identify the materials studied either as to the origin of the protein or mode of hydrolysis. A service would be rendered if such studies identified the preparations studied, whether they are commercial preparations or not. Urinary losses of amino acids with oral administration were small, but when the preparations were given intravenously, 5 to 20 per cent of the free amino acid nitrogen and 18 to 45 per cent of the peptide nitrogen administered were found in the urine, the highest peptide excretion following administration of the preparation containing the highest peptide level.

In another study the authors attempted to design amino acid mixtures so that minimal amounts of each amino acid were lost into the urine of dogs after intravenous injection. They suggest that large urinary losses indicated that the quantity of a given amino acid included was disproportionately higher than the need of the animal.

Such a concept of amino acid excretion, although certainly suggestive, does not take into consideration the renal clearances of the amino acids, which form the subject of an extensive study by L. D. Wright (*Tr. N. Y. Acad. Sci.* **10,** *271 (1948)*). In these experiments, dogs were infused at definite rates with various amino acid mixtures. Creatinine clearance was measured at the same time. Renal clearances for each of the ten so-called essential amino acids were then determined. The amino acids, leucine, isoleucine, valine, histidine, methionine, phenylalanine, and threonine all showed complete tubular reabsorption up to very high plasma levels. On the contrary, lysine and arginine were poorly absorbed following their filtration through the glomerulus. In the next part of the study pairs of amino acids were administered together. For the two amino acids, arginine and histidine, which were poorly reabsorbed, there was marked competition for reabsorption when the two were given together. Histidine, like arginine and lysine, a basic amino acid, likewise competed with these two for reabsorption. Thus the authors postulated that for these basic amino acids a separate mechanism for reabsorption was present. A second reabsorption mechanism was suggested for the mono-amino, mono-carboxylic amino acids, leucine and isoleucine. Glycine also seemed to compete with some of the other amino acids for reabsorption. With the amino acid mixtures available it was not possible to increase the rate of administration to exceed the maximal rate of tubular reabsorption in any instance. Wright also concluded that following intravenous administration the plasma amino acid concentrations were too low for marked competitive inhibition of reabsorption to occur.

Eckhardt *et al.*, studied also the excretion of amino acids by 7 patients with liver disease (5 cirrhosis, one hemochromatosis, one subacute yellow atrophy). These were observed to excrete approximately the same amounts of essential amino acids as did normal subjects, both on normal diets and after infusions of amino acid mixtures. On the other hand, 5 patients with Wilson's disease (hepatolenticular degeneration) excreted about 20 mg. of alpha-amino nitrogen hourly

compared with 5 mg. by controls. There was no apparent correlation between blood levels of amino acids, which were only slightly elevated, and the unusually large urinary levels. It was assumed that a faulty renal mechanism was operative which permitted spillage of amino acids in the fasting state, but which returned increased doses to the body after infusions.

Studies such as the foregoing are tending to place the designing of preparations for intravenous nitrogen nutrition upon a more solid footing than has characterized the earlier history of this subject.

DETERMINATION OF THE NUTRITIVE VALUE OF PROTEINS BY CHANGES IN LIVER CYTOPLASM

The biologic value of proteins may be appraised by a number of different procedures. This has been accomplished in the past by measurement of weight gain in growing animals (*Nutrition Reviews* **5,** *344* (*1947*)), by determination of plasma protein formation in protein depleted animals (*Ibid.* **1,** *200* (*1943*)), by the effect of the test protein on nitrogen balance (*Ibid.* **2,** *169* (*1944*); **4,** *29, 264* (*1946*); **6,** *269* (*1948*)), or by analysis for essential amino acids in a given protein (*Ibid.* **5,** *112* (*1947*)). More recently it has been demonstrated that the substantial and rapid decrease in weight of the rat liver which occurs during fasting or with diets low in protein is in part due to loss of protein and that the regeneration of liver protein may serve as a method of assay of the adequacy of dietary protein (*Ibid.* **4,** *309* (*1946*)).

H. W. Kosterlitz (*J. Physiol.* **106,** *194* (*1947*)) and R. M. Campbell and Kosterlitz (*Ibid.* **107,** *383* (*1948*)) provide further description of changes occurring in liver when the protein content of the diet is changed, and evaluate this procedure as a means of assay of the nutritive value of proteins. The following experimental procedure was utilized. Adult female rats approximately 4 months of age and having an average weight of 220 g. were used. Prior to the experiments these rats were maintained on a usual stock laboratory diet. The protein-free basal experimental diet consisted of 2 per cent agar, 3 per cent salt mixture, 25 per cent sucrose, 60 per cent potato starch, and 10 per cent lard. To the lard were added supplements of vitamins A, D, and E. The "B-vitamins" were supplied as a solution of the crystalline compounds. In some instances an additional supplement of liver extract was also provided. Modification of this basal diet to include protein or amino acid mixtures was accomplished by replacement of sucrose in the diet. In the nutritive appraisal of a given protein, rats were taken off the stock diet and either transferred directly to a diet containing the test protein or were given the protein-free basal diet for four days to deplete the liver of "labile cytoplasm" and then were placed on a test diet for four days.

With the institution of diets low in protein but adequate calorically and in other essential nutrients there was a rapid decrease in the concentration of protein, phospholipid, and nucleic acid in the livers of the rats studied. These changes in chemical composition were related to morphologic changes in liver cells. It was demonstrated that the small glycogen-poor cells of fasted rats contained high concentrations of protein, phospholipid, and nucleic acid. In contrast, in rats fed on a protein-free diet it was observed that the cells of the liver were but slightly decreased in size and were characterized by low concentrations of protein, phospholipid, and nucleic acid. Liver cells of rats on protein-free or low protein diets demonstrated a loss of stainable cytoplasm and a decrease in cytoplasmic structures, a change described earlier by R. Elman, M. G.

Smith, and L. A. Sachar (*Gastroenterology* **1**, *24* (*1943*)). Kosterlitz restates the fact that the chromophile ground substance and basophile granules of cytoplasm contain most of the phospholipid and ribonucleic acid of the cytoplasm and that concentrations of these substances are reduced on low protein regimens.

The sum of the contents of liver cells of protein plus phospholipid plus ribonucleic acid may then very reasonably be taken as a measure of liver cytoplasm. Such determinations, however, may be time consuming and laborious. A simpler method of assay is achieved by determination of the nonlipid nonglycogen solids (NNS) of liver. A straight line relation was shown to exist between concentration of NNS and protein plus phospholipid plus ribonucleic acid as related to initial body weight. The sum of the latter three components comprises about 90 per cent of the NNS under all of the circumstances tested. Of the total NNS in rats on the stock diet about one-third is rapidly lost on protein-free diets. This the authors refer to as "labile NNS." The remainder is stable and remains relatively unchanged by longer periods on diets deficient in protein. The decrease in NNS during the first few days on protein-free diets follows a simple exponential curve with almost total loss of labile cytoplasm within four days and nearly complete restoration after two days of feeding a 20 per cent casein diet.

Casein was selected as a standard of reference for determination of the nutritive value of other proteins. When the NNS was compared with the logarithm of daily casein intake a straight line relation was found. A daily food intake of 7.0 g. per 100 g. body weight assured full utilization of the proteins in the diet. The method was sufficiently sensitive to demonstrate that inclusion of liver extract or potato starch in the diet raised the apparent nutritive value of casein because of amino acids contained in those materials.

Having examined the conditions and modifying factors in this means of assay, the nutritive value of other proteins and amino acid mixtures was determined and compared with that of casein. When an arbitrary nutritive value of 1.0 was assigned to casein, egg albumin was found to have a nutritive value of 1.28, zein 0.25, an acid hydrolysate of casein 0.42, an enzymatic digest of casein 0.72, and an enzymatic digest of meat 1.0. The nutritive value of zein was not increased by the addition of lysine to the diet but was increased to a value of 0.89 when both tryptophan and lysine were added. The low nutritive value of acid hydrolysates of casein was increased to that of casein by addition of d,l-tryptophan to a concentration of 1.2 to 1.5 per cent. In each instance the nutritive values ascertained for these proteins compared favorably with results obtained by other methods of assay of their biologic value.

The regeneration of liver cytoplasm as determined by the nonlipid nonglycogen solids has with this information been demonstrated to be a sensitive and readily adaptable procedure for obtaining further data concerning the nutritional adequacy of proteins. This type of analysis is accomplished with relatively little expenditure of time and effort on the part of the investigator. The variability of results is not great and compares with that achieved by other methods. It should be pointed out, however, that there may be variations in the biologic value of a given protein for different species and for different physiologic phenomena. Information presently available indicates that of the amino acids commonly found as constituents of dietary proteins, ten are essential for growth of the rat while only eight are required to maintain nitrogen balance in young adults. One should be cautious in assuming that the nutritive value of a protein for man is identical with that as determined in the experimental animal.

TRANSFER OF IMMUNITY FROM COLOSTRUM TO THE NEWBORN CALF

The relations of the globulins of colostrum to the composition of the serum proteins and to the passive immunity of the newborn calf have been the subjects of a variety of investigations during the past three decades. E. Jameson, C. Alvarez-Tostado, and H. H. Sortor (*Proc. Soc. Exp. Biol. Med.* **51,** *163 (1942)*) and C. L. San Clemente and I. F. Huddleson (*Mich. Agr. Exp. Sta. Bull.* **182,** *3 (1943)*) demonstrated that the serum of the newborn calf does not contain an appreciable amount of gamma-globulin and that the appearance of a serum globulin which has a low electrophoretic mobility follows the feeding of colostrum. The immune lactoglobulin of colostrum has been shown to differ substantially from the gamma-globulin of cow serum in electrophoretic mobility and in properties of passive immunity (E. L. Smith, *J. Biol. Chem.* **164,** *345 (1946)*; **165,** *665 (1946)*; Smith, R. D. Greene, and E. Bartner, *Ibid.* **164,** *359 (1946)*; Smith and N. H. Coy, *Ibid.* **164,** *367 (1946)*; Smith and Greene, *Ibid.* **171,** *355 (1947)*).

R. G. Hansen and P. H. Phillips (*J. Biol. Chem.* **171,** *223 (1947)*) have studied the relation of the time of ingestion of colostrum to the level and distribution of blood serum proteins by the newborn calf. Electrophoretic analyses to differentiate the various protein components of the serum were made with a modified Tiselius apparatus. The values for distribution and mobility of each protein fraction were made from measurements of an enlarged tracing of the photograph of the boundary. These investigators also observed that calves which were removed from their mothers soon after birth and not allowed access to any colostrum had negligible amounts of serum gamma-globulin. When these calves were fed skim milk fortified with ample amounts of vitamin A and ascorbic acid, very low but gradually increasing amounts of serum gamma-globulin were observed. By 8 weeks of age, the gamma-globulin component comprised 18.0 per cent of the serum proteins. Concurrent with this increase, there was a relative decrease in the alpha-globulin fraction of the serum proteins from 37.6 to 22.9 per cent. By way of contrast, when colostrum was fed at a level of 5 pounds per 100 pounds of body weight to 3 newborn calves within 12 hours after birth, a slow moving component was observed to comprise 19.6, 22.2, and 24.0 per cent, respectively, of the serum proteins within 24 hours. When the same amount of colostrum was fed to 2 calves at 24 hours of age, the levels of this slow moving protein component increased to 9.7 and 10.7 per cent, respectively. When colostrum at the same level was fed to calves more than 24 hours of age, no appreciable amount of this slow moving protein could be detected in the serum.

To test the relation of the water soluble globulin in colostrum to the slow moving protein introduced into the serum after colostrum feeding during the first 24 hours of life, Hansen and Phillips prepared some of this globulin from colostrum by the method of E. L. Smith (*J. Biol. Chem.* **164,** *345 (1946)*). When 40 g. of this preparation were given to a newborn calf, the percentage of the slow moving protein component of the serum was found to be 7.6 per cent. In a second newborn calf which was given 70 g., the level in the serum was 11.5 per cent of the total proteins. However, administration of 70 g. of this water soluble globulin to a calf 3 weeks of age which had had no colostrum previously did not result in any increase in the slow moving component of the serum proteins. These investigations demonstrated the ability of the newborn calf to absorb this protein moiety directly from the intestinal tract during the first 24 hours of its life and an almost complete inability to do this beyond that age.

E. L. Smith and A. Holm (*J. Biol. Chem.* **175,** *349 (1948)*) have made various tests to determine whether the new protein which

appears in the serum after the ingestion of colostrum by the newborn calf has the same electrophoretic properties as colostrum and whether this protein is changed during its passage from the intestine of the calf to the blood stream. Observations of the serum proteins of 3 newborn calves were made at birth and at varying periods after feeding of colostrum. The serum of the newborn calves did not contain gamma-globulin nor T-globulin. None of the antibodies present in the serum of the mothers could be demonstrated in the serum of the calf; this indicated that there had been no transfer of antibodies across the placenta in the bovine species. After ingestion of colostrum, a new component appeared among the serum proteins which was slow moving with a mobility of 2.1×10^{-5} sq. cm. per volt per second in veronal buffer at a pH of 8.4. This component had retained the characteristic mobility of the immune lactoglobulin of colostrum during and after its passage from the intestinal tract to the blood. Since the mobilities of the gamma-globulin and of the T-globulin of hyperimmune maternal bovine serum were reported to be 1.3×10^{-5} and 2.5×10^{-5}, respectively, when determined under the same conditions as the colostrum globulin, these investigators concluded that this new component of calf serum proteins was not a gamma-globulin. About the fiftieth day, a distinct peak, which had the characteristics of gamma-globulin, was observed to appear in the electrophoretic pattern of the calf serum. By the one hundred and twenty-second day this peak had become pronounced. During this period the peak for colostrum globulin had been gradually diminishing, but on the one hundred and twenty-second day it was still a discrete, although very small entity.

The role that colostrum ingestion by the newborn calf played in the development of passive immunity against infectious disease was demonstrated by T. Smith and R. B. Little (*J. Exp. Med.* **36,** *181 (1922)*) and by T. Smith and M. L. Orcutt (*Ibid.* **41,** *89 (1925)*). In the current investigations, E. L. Smith and Holm (*loc. cit.*) used colostrum from cows which had been hyperimmunized with a mixture of the antigens, diphtheria toxin or toxoid, vaccinia virus, and a killed culture of Hemophilus pertussis. The immune activity of the colostrum and of the serum of the calves to which colostrum had been fed was determined. Assays of diphtheria antitoxin were performed by the rabbit skin test described by C. Jensen (*Acta path. et microbiol. Scandinav.* (*Suppl.*) **14** (*1933*)). Determinations for pertussis antibodies were made in terms of mouse-protective units by a modification of the method of N. Silverthorne (*Canad. Pub. Health J.* **29,** *233 (1938)*). Vaccinia assays were made with rabbits by a skin test that had been perfected in the investigators' laboratory. Colostrum was found to have the following immune properties per cubic centimeter: 80 units of diphtheria antitoxin, 190 units of Hemophilus pertussis antibodies, and 6400 neutralizing skin test doses of vaccinia virus antibodies. At birth, calf serum was found to contain no Hemophilus pertussis antibodies and no vaccinia virus antibodies and less than 0.001 unit per milliliter of diphtheria antitoxin. Two days after feeding the above sample of colostrum, calf serum contained 40 units per milliliter of diphtheria antitoxin, 70 units per milliliter of Hemophilus pertussis antibody, and 6400 neutralizing skin test doses per milliliter of vaccinia virus antibody. Progressive decreases in these values were noted on the fiftieth and eighty-seventh days. On the one hundred and twenty-second day, the values were still lower; calf serum then contained 0.6 unit per milliliter of diphtheria antitoxin, 16 units per milliliter of Hemophilus pertussis antibody, and 800 neutralizing skin test doses of vaccinia virus antibody per milliliter. Smith and Holm drew attention to the fact that human beings are regarded as immune to diphtheria when the Schick test is negative, which test reflects a serum level of as little as 0.03 unit of

antitoxin per milliliter. For the calf described above, the level of diphtheria antitoxin derived from colostrum still was far in excess of this amount even after four months. The importance of colostrum for the development of passive immunity in the calf is evident from these data. In nature, the effect might be even still greater if the calf were allowed to suckle without restriction.

Observations were also made on the serums of a newborn lamb, a 3 day old lamb, and the mother. The serum of the newborn lamb closely resembled that of the newborn calf with respect to the slow moving protein components. In addition to the appearance of colostrum globulin in the serums of the 3 day old lamb, there was a definite increase in the beta-globulins, and considerable changes in the relative amounts of the alpha-globulins.

In contrast to the absence of gamma-globulin in the serums of the newborn calf and lamb, the level of gamma-globulin has been demonstrated to be slightly higher in the serums of the newborn human infant than in the serums of the mother (L. G. Longsworth, R. M. Curtis, and R. H. Pembroke, *J. Clin. Invest.* **24,** *46 (1945)*). This would help to explain the presence of antibodies in the human infant and would point to a definite placental transfer of antibodies and gamma-globulin in the human species.

Electrophoretic examination of the serums of newborn offspring of various species appears to be a readily applied, accurate method for studying placental transfer of antibodies. Actually little is known of this process in human beings and still less is known of the possible value of colostrum to the human infant for the development of certain types of passive immunity.

USEFULNESS OF STRESS IN EXPERIMENTAL NUTRITION STUDIES

Reflection upon the trends in experimental studies in nutrition reveals that activities have progressed along certain fronts. Caloric nutrition was probably the first such front; followed by studies of nitrogen and protein metabolism, later refined more specifically to amino acid metabolism. Recognition of and studies on those minerals required in relatively large amounts were later refined to investigations of so-called "trace elements." Early in this century the "accessory substance front" began and the initial studies dealt with those accessory factors a deficiency of which could be most readily and conveniently produced in laboratory animals.

The variety of experimental conditions which have been employed in studies of the vitamins or accessory factors during the past four decades make it appear reasonable that most of the deficiencies detectable by classic methods of study have been recognized. This statement does not imply, however, that all of the nutritive essentials have been uncovered. Technics which consist of adding stresses to the organism have already succeeded in producing evidence of the effect of hitherto unrecognized accessory factors. One of the more successful of these technics involves the addition of desiccated thyroid to experimental diets. The earlier studies employing this technic dealt with the effect of vitamin supplements to hyperthyroid animals which had lost weight, in an effort to determine whether these additions would permit the animals to regain their lost weight. Evidence accumulated that thiamine, pyridoxine, and pantothenic acid exerted such an effect in dogs or adult rats (V. A. Drill, *Physiol. Rev.* **23,** *355 (1943)*; *Nutrition Reviews* **2,** *87 (1944)*).

An even greater stress may be placed on experimental animals by the administration of thyroid to the growing animal. Increased

requirements under these conditions might be expected to be more pronounced than in hyperthyroidism induced in the adult rat (*Nutrition Reviews* **6,** *54* (*1948*)). Considerable additional data on these studies have now appeared (B. H. Ershoff, *Arch. Biochem.* **15,** *365* (*1947*)). In this work, Ershoff used the same basal diets as previously employed. Diets A and B were purified rations that contained vitamin B-complex factors in synthetic form and which differed only in that Diet B contained niacin, while Diet A did not. Diet C was of similar composition but contained yeast in place of the synthetic "B-vitamins." The amounts of "B-vitamins" (thiamine, riboflavin, pyridoxine, pantothenic acid, niacin, choline) in all the diets were adjusted to the level contained in the yeast-containing ration. Two groups of animals were studied on each dietary regimen; one receiving no supplementary thyroid, the other 0.5 per cent U.S.P. desiccated thyroid in the diet. Both sexes and two separate strains of animals were employed. The rats were placed on experimental regimens at 21 to 30 days of age and weighed approximately 45 to 55 g. Survival studies over a period of one hundred and sixty-eight days were made. The average survival length for one series of female animals was 51.7, 52.4, and 101.2 days respectively for the thyroid-containing diet without niacin, with added niacin, and with yeast. Inasmuch as these three diets contained equal amounts of thiamine, riboflavin, pyridoxine, and pantothenic acid, the beneficial effect of the yeast could not be due to these substances. All animals fed the thyroid-free rations survived the entire experimental period of one hundred and sixty-eight days. These results confirmed the earlier conclusions that yeast contains a substance which promotes survival of thyroid-fed rats.

When death occurred in the thyroid-treated rats the immediate cause appeared to be heart failure. Heart weights were found to be increased and there was hypertrophy of the ventricular wall. Chemically, there was marked reduction in creatine content of cardiac muscle—the concentration of ventricular creatine in thyroid-fed rats averaged approximately half that of animals on the same diet without added thyroid. However, there was no significant difference in creatine concentration of heart muscle between the yeast supplemented and unsupplemented rats fed on thyroid. The addition of yeast did not prevent the development of diarrhea or the dull, rough, and dirty appearance of the fur in thyroid-fed rats. It is implied that both these findings, however, were less severe in the yeast-fed group. Gonadal development was inhibited in the yeast-supplemented as well as unsupplemented thyroid-fed rats. This is in agreement with previous reports (*Nutrition Reviews* **6,** *54* (*1948*)).

Another criterion for the study of such animals is growth. Retardation of growth is an almost universal sign of nutritional deficiencies. It might be reasoned, therefore, that the retardation of growth observed in thyroid feeding may be a manifestation of a deficiency of some nutrient precipitated in the young rat. To test this point, animals in groups of 10 to 30 each were placed on the thyroid-niacin-containing diet described above. Observations on weight were made for a hundred days or until death occurred. The effects on growth and survival time of addition of any of the number of crude substances to the dietary regimen may be summarized as follows: Survival time was significantly greater in the groups receiving yeast, whole liver, autoclaved whole liver powder, or an extracted liver residue. The shortest survival time was seen on a diet containing pancreas. The greatest weight gains occurred in those animals whose diets were supplemented with whole liver powder, autoclaved whole liver powder, or the extracted liver residue. Although the addition of yeast to the diet containing thyroid improved survival time, it did not appreciably increase the weight gains of the animals.

To test whether these influences on survival time and weight gain of crude materials might be due to supplying any of the recognized vitamins, a series of animals was studied in which the same thyroid-containing diet was fed, but increased amounts of each of the known vitamins were added individually. The effect was determined of additions of other known factors, including biotin, folic acid, tocopherol, creatine, methionine, but not vitamin B_{12}. It was concluded that none of these known substances fed alone as supplements improved either growth or survival under the test conditions. Careful examination of the data gives some indication that biotin may have had a slightly beneficial effect, but the effect is not statistically significant. The effect of the simultaneous feeding of all of these factors was not determined.

The author states that a water-extractable 1:20 liver concentrate (Wilson) had virtually no activity in respect to prolongation of survival or promotion of growth in the immature thyroid-fed rat. On the other hand, the extracted liver residue had both growth-promoting and survival-prolonging effects. This finding may be of considerable importance since J. J. Betheil, V. D. Wiebelhaus, and H. A. Lardy (*J. Nutrition* **34**, *431* (*1947*)) found that this same 1:20 liver powder exerted definite weight-increasing properties under the conditions of their studies on immature thyroid-fed rats. These differences in observation may reside in slight differences in experimental technic or may indicate a multiplicity of substances which are active in the thyroid-fed rat.

Ershoff has attempted to establish the point of action of the hypothesized factor in liver and yeast. He reasoned that the three following processes could be involved: (1) an increase in food consumption, (2) an increased efficiency of utilization of food, and (3) direct antithyroid hormone activity. Determinations of the basal metabolic rate of rats fed the thyroid-containing diet plus yeast or liver revealed no significant difference between liver- and yeast-fed rats. Accordingly, it was concluded that the growth stimulation of liver was not mediated through direct antithyroid hormone activity of the liver. On the other hand, it was found that the yeast-thyroid-fed rats ate slightly more than the thyroid-fed controls and that liver-thyroid-fed rats ate considerably more than either of the other groups. Thus, the total food intake per rat for a twenty-eight day period on the thyroid diet alone was 327 g.; on the diet plus yeast, 366 g.; on the diet plus liver, 417 g. The efficiency of food utilization, expressed as average gain in weight per gram of food eaten, was greatest for the liver-fed animals.

Ershoff has interpreted his studies to indicate that the excessive doses of thyroid bring about increased requirements in the immature rat for one or more unknown nutrients. Failure to provide this nutrient in adequate amounts results in a deficiency syndrome manifest by retarded growth, inhibition of gonadal development, and early death due to cardiac failure. The deficiency can be prevented by a factor or factors present in whole liver. Yeast prolongs the survival age of animals on the thyroid-containing ration. None of the well known nutrient essentials protects the thyroid-fed rat. The value of such stress studies as a tool in nutritional investigation is illustrated by these investigations of Ershoff.

A number of growth effects has been ascribed to preparations from liver. A variety of names has been applied to these hypothesized new factors. One of the best established is the animal protein factor (*Nutrition Reviews* **6**, *219* (*1948*)). Vitamin B_{12} (*Ibid.* **6**, *245*, *291* (*1948*)) plays a dominant role in discussions related to these newer factors. In fact it was recently announced that vitamin B_{12} and the animal protein factor were identical (E. L. Rickes *et al.*, *Science* **108**, *634* (*1948*)). Other observations which may be related to Ershoff's experiments are the obesity-provoking effect of liver when fed to rats on a diet containing

sulfaguanidine (G. A. Emerson, *Federation Proceedings* **4,** *117 (1945)*) and the hematopoietic activity of certain liver extracts for low protein-fed, sulfathiazole-treated rats (G. A. Emerson and C. W. Mushett, *Ibid.* **7,** *285 (1948)*). Again, it is to be noted that the evidence for the existence of these factors has come largely from studies employing one or another type of stress condition. This developing front in nutrition research bears consideration as a mode of attack on a variety of problems.

HUNGER AND HUMAN BEHAVIOR

Physiologic and psychologic changes in man as a result of prolonged starvation have been studied by a number of workers, particularly in recent years as a result of the widespread famine conditions which have prevailed in many parts of the world (*Nutrition Reviews* **3,** *95, 96, 225 (1945)*; **5,** *28 (1947)*; **6,** *279 (1948)*). In the study of large population groups, controlled experimentation during depletion is, of course, impossible, and the details of starvation have remained largely unknown. Because of this, and to determine the relative effectiveness of different types of diet in bringing about rehabilitation, a large-scale experiment was begun in 1944 at the University of Minnesota, using conscientious objectors as volunteer subjects.

In outlining the background of the experiment, J. C. Franklin, B. C. Schiele, J. Brozek, and A. Keys (*J. Clin. Psychol.* **4,** *28 (1948)*) stated that 36 "normal" young men between the ages of 20 and 33 years (mean, 25.5 years) were recruited from over a hundred applicants who prior to the experiment had participated in various projects of national importance under the Civilian Public Service program. Men finally included were screened according to freedom from history of disabling diseases including mental illnesses, absence of physical defects, willingness to subordinate personal interests and activities to the requirements of the experimental program, active interest in problems of nutritional relief and rehabilitation, and freedom from family responsibilities. It was reported that the men were highly regarded by their associates and the authors felt that any sample-bias present in the findings would err on the conservative side, since the psychobiologic stamina of the subjects was considered superior to that which might be found in a group selected at random. The men selected represented, within normal limits, a wide range of individual differences in body build, physical fitness, and personality. Control observations were made during three months, in which the subjects were maintained on a "good" diet which provided an average of 3492 calories per day. Six months of semistarvation followed in which the intake was reduced to an average of 1570 calories. The diet was planned to simulate that available in Western and Central Europe under the conditions of food shortage during the war, and was calculated to produce a weight loss of about 25 per cent over the period. Individual fluctuations in the caloric levels were made to compensate for too slow or too rapid loss in weight. Three months rehabilitation followed, in which the men were divided into four groups, receiving additional allotments of approximately 0, 400, 800, and 1200 calories.

At the end of the semistarvation period, the average weight loss was 24 per cent, with some of the actual body weight loss being masked by accumulation of edematous fluid, especially in the ankles, knees, and face. The subjects reported that their nails grew more slowly, their hair was falling out in greater quantities, and wounds, such as shaving cuts, healed more slowly. Tolerance to heat increased as starvation progressed; the food was required unusually hot, and during the summer the subjects slept under blankets and wore extra clothing during the daytime. Objective tests revealed

no decrease in visual acuity, but many complaints were registered of inability to focus, eye aches, and "spots" before the eyes. Overt movements became noticeably slower, and voluntary energy output was considerably reduced, although scheduled physical activity was maintained, including housekeeping chores and walking about twenty miles per week. The subjects described their increasing weakness, loss of ambition, narrowness of interests, depression, irritability, and loss of libido as a pattern of experience characteristic of aging.

Anticipation of eating heightened the craving for food. As a result, the men resented waiting in line while their meals were measured and weighed, and their attitude toward food became very possessive. Some hovered over their trays with their arms placed in a protective manner. While eating, the subjects were silent and deliberate. Many attempts were made to make the food appear to go further, for example, by adding hot water to soup, removing the fluid and repeating the process before eating the solid portion of the soup, or by "souping" solid foods in order to increase their bulk. Satisfaction was also obtained by the use of large quantities of coffee and tea, even among those who previously did not use these beverages. Chewing gum was employed heavily, and smoking was increased both in degree and in numbers of participants. Food in all its ramifications became the chief topic of conversations, reading, and daydreams. Such things as cook books, recipes, and cooking utensils were very popular, and some of the subjects replanned their lives toward agriculture or cooking as vocations. Some, on the other hand, reacted bitterly toward this "tyranny" of food. Nevertheless, it is reported that adherence to the diet was strict. Four out of the 36 participants partook of additional food, and were dropped from the experiment. It was felt that the high proportion of adherents was in part due to the fact that the subjects were thoroughly aware of the importance of their participation and the likely importance of the experiment as a whole. Many hoped to go to Europe on rehabilitation and relief teams, and felt that firsthand starvation experiences would render them more effective.

The prolonged strain upon the subjects was reflected in increased emotional instability. B. C. Schiele and J. Brozek (*Psychosomat. Med.* **10,** *31 (1948)*), using the Minnesota Multiphasic Personality Inventory found that tendencies toward depression, hysteria, and hypochondriasis were markedly increased, whereas five other traits (psychopathic deviation, paranoid reaction, psychasthenia, schizophrenia, and mania) were affected only slightly. All these personality characteristics were normal at the start of the experiment. Of the three tendencies affected, depression seemed most pronounced. Although pathologic proportions were reached in only a few individuals, the men were reported to be more serious and obviously less happy than during the control period. Occasional spells of elation appeared, lasting for a few hours or days, but these were always followed by "low" periods. Other characteristics described were general apathy toward topics which formerly held the subjects' interest. The high group morale, which had been an outstanding characteristic during standardization, gradually disappeared. Such humor as remained became of the ironic and sarcastic variety. General intelligence seemed unaffected, although the educational program designed to prepare the men for foreign relief work, which had been received at the start with enthusiasm, was gradually neglected and finally discontinued. The subjects regarded their nonstarved associates with increasing resentment, and developed a sense of belonging to a group apart from nonstarved people.

During the rehabilitation period, progress of recovery was slow. At the end of twelve weeks, the subjects in the highest calory

group (1200 calories in addition to the basal rehabilitation diet) had regained only 60 per cent of the weight lost. Those in the 400 calory group gained no weight during the first six weeks and after twelve weeks they had regained only 20 per cent of the weight lost. Some of the subjects actually lost weight during the early part of the rehabilitation period, due to disappearance of the edema. Recovery from dizziness, apathy, and lethargy was most rapid, whereas tiredness, weakness, and loss of sex drive were slow to improve. Cramps and paresthesias were unrelieved at the start, and new complaints appeared, such as distention, belching, flatus, and stomach-ache. Physical capacity resembling that of the prestarvation state was approached only after six months rehabilitation. Meanwhile, appetites were insatiable, and many of the food fetishes which had developed during starvation continued. The slow recovery, contrasted with that which the subjects had expected to be rapid, made many of them actually more depressed and irritable than before.

An important feature of this study, mentioned by the authors and by O. R. Chambers (*Chem. Eng. News* **26,** *2872 (1948)*), dealing with group behavior, has far-reaching implications in the socio-political field. At the start of the experiment, the group was characterized by good humor, friendliness, and fellowship; democratic principles and spirit guided them in their actions. As the starvation period proceeded, the men lost some of their ability to make rational decisions. In 3, possibly 4 men, finally dropped from the experiment, the moral fiber degraded to the point where some stealing of food occurred. Regulations which were questioned as to their merits at first, became accepted without challenge as starvation proceeded; leadership and initiative among the men disappeared completely and they welcomed a firm direction. Starvation made them submissive. In the early phases of rehabilitation the prevailing mood was that of rebelliousness and hostility.

Several men began to doubt the value of the project and the motives and competence of those conducting the experiment. The morale of the group was very low. The "buddy" system which had been maintained whenever the subjects left the laboratory, chiefly to checkmate against the partaking of extra food, had to be removed at the end of the sixth week of rehabilitation in order to avoid wholesale violation. Toward the end of the rehabilitation period, the morale was noticeably improved, and the men began to look forward to developing their own plans for the future.

At the end of the twelfth week of rehabilitation, 20 of the men were permitted absolute freedom in their food intake. The response was immediate, with 6000 to 7000 calories per day being ingested. Many ate more or less continuously for two days, and continued to eat at high levels, so that at thirty-three and fifty-five weeks after the end of the starvation period they exceeded their prestarvation weights.

It was recognized that this experiment could not duplicate the conditions usually found in mass starvation. The experimental subjects did not suffer from fluctuations in food supply nor from the anxiety caused by political turmoil, threat of sudden death or injury, or destruction of property. On the other hand, they were starving in the midst of plenty, and it was felt that part of the stress upon the individuals must have come from the knowledge that, as volunteers, there was no compulsion to continue the diet. Nevertheless, the authors cite references to indicate that the symptoms observed here duplicate in large measure the observations taken of mass starvation in internment camps of Southern France, at the beseiged Leningrad, in India, in Holland, and at the concentration camps in Germany. These observations point inescapably to the importance of nutrition in shaping world governments. It is a fact that democracy has never existed in a country where there was not adequacy of food.

MECHANISM OF ACTION OF ANTIMETABOLITES

Antimetabolites are substances which by virtue of their similar chemical structure to essential substances in the cell interfere with the utilization of these substances and thus adversely affect cell function and growth. Antimetabolites are often termed "analogues," and various types are recognized. Thus malonic acid might be termed a substrate (succinic acid) analogue, ethionine and thienylalanine as amino acid analogues (*Nutrition Reviews* **3,** *340 (1945)*; **4,** *70 (1946)*), and pantoyltaurine, pyrithiamine, and many others as vitamin analogues.

Interest in vitamin analogues arises from several quarters. To the physician they represent possible new agents in the treatment of disease, to the pharmacologist a principle for a directed search for new specific drugs, to the nutritionist tools for the production of vitamin deficiencies and an understanding of vitamin function, and to the biochemist they are possible specific inhibitors of enzyme function which may aid in dissecting metabolic events in the cell.

The most plausible theory for the action of a vitamin analogue is that it displaces the vitamin from an enzyme with which it is normally engaged in metabolism. The union of substrate or coenzyme with the protein portion of an enzyme is not new in biochemistry, and "displacement" of the normal substance by an analogue is not without precedent. A vitamin may become associated with an enzyme in at least two ways: (a) it may become associated in the process of synthesizing the vitamin into the active coenzyme molecule, or (b) it may make the union in the form of the active coenzyme. The literature reveals that vitamin inhibitors are more concerned with the synthesis of the vitamin into a metabolically active coenzyme form, there being few examples of a direct inhibition of coenzyme function by vitamin analogues (the mechanism of antimetabolite action is more fully discussed by D. W. Woolley (*Physiol. Rev.* **27,** *308 (1947)*). Inhibitors of the direct coenzyme function of a vitamin should probably be structural analogues of the coenzyme itself since the nonvitamin portions of the coenzyme molecule may be principally involved in the union of the coenzyme with protein to form the active enzyme. Without these attaching groups the inhibitor would be ineffective in displacing the coenzyme.

The mode of action of the individual vitamin analogues has not been studied in detail. However, A. E. Axelrod, S. E. Purvis, and K. Hofmann (*J. Biol. Chem.* **176,** *695 (1948)*) have now published a paper which is concerned with the mechanism of action of biotin analogues. Certain biotin analogues had been demonstrated in their laboratory to be biotin inhibitors in the growth of several microorganisms. R. J. Winzler, D. Burk, and V. du Vigneaud (*Arch. Biochem.* **5,** *25 (1944)*) had previously demonstrated that the fermentation rate of biotin deficient yeast was found to be greatly increased by the addition of biotin to the medium. Biotin has been implicated (*Nutrition Reviews* **5,** *346, 355 (1947)*) as part of a coenzyme involved in the enzymatic formation of oxalacetate and aspartic acid, presumably from pyruvate.

The experiments of Axelrod, Purvis, and Hofmann utilized the yeast fermentation system in studies of the action of biotin analogues. The fermentation of biotin deficient yeast was markedly accelerated by addition of biotin to the medium, in confirmation of earlier results. This effect was absent when the biotin analogues (oxybiotinsulfonic acid, homooxybiotin, and gamma [3,4-Ureylene cyclohexyl]-butyric acid) were added prior to addition of the biotin. In contrast, once biotin had established the increased fermentation rate, these inhibitors did not have a direct inhibitory effect on fermentation. Thus it appears that the action of the biotin analogues was to inhibit the incorporation of biotin into an active coenzyme, but not to inhibit directly the

function of the coenzyme in the fermentation process. Of interest was the finding that aspartic acid, a presumed product of the reaction catalyzed by the biotin-containing coenzyme, was able to stimulate the fermentation in the absence of added biotin, and further that this stimulation was not affected by the biotin analogues.

This work establishes that in the biotin analogues selected they "antagonize" or inhibit biotin by blocking the synthesis of the enzymatically active complex (or coenzyme) containing biotin, rather than by inhibiting directly the function of the biotin coenzyme in its role in yeast fermentation.

EFFECT OF VARIOUS NUTRIENTS ON THE GROWTH OF ROUS SARCOMA

It is reasonable to assume that the rapidly dividing cells of malignant tissue have metabolic and nutritional requirements at variance with those of cells of normal tissue (*Nutrition Reviews* **4,** *353* (*1946*)). Readily transmittible tumors of experimental animals provide means whereby study may be made of these differences. It is also possible by such means to examine the effect of the nutrition of the host on the development and rate of growth of tumors. P. A. Little, J. J. Oleson, and Y. SubbaRow (*J. Lab. Clin. Med.* **33,** *1139* (*1948*)) have evaluated the effects of certain dietary constituents on the Rous sarcoma of chickens. This tumor offers particular advantages for investigations of this type. It is transmitted easily and quickly to young chicks. Under favorable laboratory conditions small inoculums of the suspended tumor tissue will bring about genesis of tumors in all inoculated animals after a nearly constant latent period. The authors used 1-day-old New Hampshire Red chicks of a selected flock. Chicks were fed a synthetic diet. The tumor response on this diet was the same as that observed on a commercial chick starter. Inoculation was achieved by injection into the right breast of 0.25 ml. of a suspension containing 1 mg. of homogenized tumor tissue in 2 per cent peptone. Under these conditions and with the complete diet, palpable tumors occurred in 100 per cent of the chicks with an average latent period of nine and a half days. The effect of a given nutrient was determined by comparing the incidence of tumors in groups of chicks fed the complete diet with that in groups fed the same diet from which the nutrient was excluded. Ten to 65 chicks were included in a test group. Observations and comparisons were made at two day intervals from the eighth to the sixteenth day after inoculation. At the end of this period all of the chicks on the complete diet had developed sarcomas.

Evaluation was made of the effects of water soluble vitamins in the diet on the response of chicks to the virus of the Rous sarcoma. Exclusion of biotin, inositol, or para-aminobenzoic acid from the diet had no effect on the incidence or rate of growth of the tumor. Deficiencies of thiamine, pyridoxine, and calcium pantothenate are severe and are rapidly produced in the young chick. For this reason chicks on diets deficient in these vitamins were given supplements on the tenth day to permit survival. Growth of the tumor was slowed by deficiencies of thiamine and calcium pantothenate but no over-all effect was noted in incidence by the sixteenth day, six days after supplementation of the diet had been effected. Incidence of tumors in chicks on diets without riboflavin was only one-third that of chicks on diets containing this vitamin. Diets deficient in nicotinamide produced slowing of tumor growth and a decrease in final incidence to one-half that found on the complete diet. Exclusion of folic acid from the diet completely inhibited growth of the Rous sarcoma, a finding which had been previously reported (P. A. Little *et al.*, *Tr. N. Y. Acad. Sci.* (*Series 2*) **10,** *91* (*1948*)).

In a similar experiment, the effects of the

fat soluble vitamins, A, D, E, and K were tested. None of these vitamins present in the diet caused stimulation in tumor growth when supplied in propylene glycol. When all of the fat soluble vitamins were combined in soybean oil there was slight enhancement of tumor growth.

Of a group of twelve different fats and oils tested, none was found to stimulate tumor growth. However, soybean lecithin, cod liver oil, and linoleic acid appeared to produce some inhibition. Cholic acid was found to influence the growth of the Rous sarcoma in much the same manner and degree as did riboflavin.

Of all dietary constituents found to affect the growth of this tumor in chicks the most profound effect was that of folic acid, deficiency of this vitamin producing complete inhibition. It has been further demonstrated that folic acid antagonists are similarly effective as inhibitors (P. A. Little, A. Sampath, and Y. SubbaRow, *J. Lab. Clin. Med.* **33,** *1144 (1948)*). Antagonists best adapted for this purpose were 4-amino-pteroylaspartic acid, 4-amino-pteroyl d(−) glutamic acid, and 4-amino-pteroylglutamic acid. The inhibitor effect on the tumor was noted before signs of severe deficiency of the vitamin were observed in the animal. However, toxicity of the antagonists was marked and appeared to be due to vitamin deficiency resulting from intensive treatment. With the administration of 4-amino-pteroylaspartic acid or 4-amino-pteroyl d(−)glutamic acid, it was possible to control the amount of folic acid available for tumor growth without depriving the chick of amounts of the vitamin required for health.

Diets deficient in specific nutrients often are associated with loss of appetite and decrease in caloric intake. It has been demonstrated that reduction of the diet to two-thirds its caloric content brings about a depression of growth of inoculated tumors (*Nutrition Reviews* **1,** *144 (1943)*). It is to be regretted that Little and his associates made no attempt to provide equicaloric feeding in the groups of chicks in which the effects of single nutrients were being appraised. It is likely that certain of the effects described by them might be modified in face of this consideration.

It is probably hazardous to assume that malignant cells originating from different tissues have similar growth characteristics and needs. In contrast to the observation that riboflavin stimulates the growth of the Rous sarcoma in chicks, is the finding that the development of liver tumors in rats fed azo dyes is inhibited by supplying extra quantities of riboflavin (D. L. Miner, J. A. Miller, C. A. Baumann, and H. P. Rusch, *Cancer Research* **3,** *296 (1943)*). However, information relating to the metabolic characteristics and requirements of tumor cells provides a valuable avenue of approach to the understanding of neoplastic growth and may conceivably lead to evolution of new procedures of treatment and control of cancer.

NIACIN, FOLIC ACID, AND LIVER EXTRACTS

Evidence that the effect of niacin in the prevention and cure of blacktongue may be associated with the presence of other dietary factors has been accumulating since the demonstration that this antipellagric vitamin is essential for the dog (C. A. Elvehjem, R. J. Madden, F. M. Strong, and D. W. Woolley, *J. Biol. Chem.* **123,** *137 (1938)*). Whereas niacin was uniformly successful in animals fed the blacktongue-producing diets composed of natural but niacin-poor foodstuffs, this was not always so if purified dietary ingredients were employed (*Nutrition Reviews* **1,** *68 (1943)*). Inhibition of the beneficial action of niacin also resulted from the addition of a sulfa compound, such as sulfa-

pyridine, to the diet (R. West, *Proc. Soc. Exp. Biol. Med.* **46,** *369* (*1941*)). In this instance, the interference with growth and the concomitant vitamin-synthesizing activity of intestinal microorganisms appeared to have the same effect as the removal of one or more dietary essentials from the food mixture (*Nutrition Reviews* **1,** *341* (*1943*); **2,** *103*, *221* (*1944*)). The effect of the sulfapyridine, in turn, was offset by supplements of fresh liver and of milk. A specific substance appeared to be involved when it was demonstrated that folic acid improved the response of niacin in deficient diets containing sulfapyridine (*Ibid.* **5,** *205* (*1947*)).

Prior to the recognition of the indispensability of niacin, it was noted that progressive macrocytic anemia characterized blacktongue in dogs. However, if this syndrome was produced in animals on a purified ration, some were found to be resistant to niacin. A combined supplement of niacin and folic acid was more effective but did not fully restore the hemoglobin level (*Nutrition Reviews* **5,** *205* (*1947*)). It has now been shown that commercial preparations of the antipernicious anemia factor bring about complete restoration of hemoglobin levels and permit growth in dogs on a purified blacktongue-producing diet if used in conjunction with niacin and folic acid (W. R. Ruegamer, W. L. Brickson, N. J. Torbet, and C. A. Elvehjem, *J. Nutrition* **36,** *425* (*1948*)).

Sulfasuxidine was employed to exaggerate the dietary deficiencies which result in weanling puppies on a diet containing casein, sucrose, cottonseed oil, salts, and vitamins. The latter were limited to vitamins A and D and to thiamine, riboflavin, pyridoxine, calcium pantothenate, and choline. Weight declined rapidly on this mixture and niacin therapy was necessary after fourteen to eighteen days. Single doses of 25 mg. of niacin resulted in a marked but temporary gain in weight. Subsequent single administrations had varying effects on the weight curve. However, in each animal a point was reached where there was no growth response to the niacin supplement. At this time it was noted that a severe macrocytic anemia was present. Hemoglobin levels varied from 8 to 12 g. per cent, the red cell count from 2 to 3 million, and the cell volume from 20 to 30 per cent. The addition of folic acid (0.1 mg. daily) together with niacin brought about some increase in weight but failed to affect the anemia.

The dogs showed many of the symptoms observed in human pernicious anemia. In addition to macrocytic anemia, the animals developed weakness, diarrhea, and a flaccid type of paralysis that was fatal. For this reason and because of the known efficacy of fresh liver and of commercial antipernicious anemia preparations in patients in whom folic acid is only partially effective (*Nutrition Reviews* **3,** *154* (*1945*); **4,** *102* (*1946*); **5,** *115*, *274* (*1947*); **6,** *90* (*1948*)), antipernicious anemia fractions were administered with niacin and folic acid. Care was taken to use dogs that had maintained weight and hematologic plateaus for thirty days on the basal diet supplemented with both niacin and folic acid. The combination of the three supplements was effective in the restoration of the blood picture and of the general health of the animals. Without folic acid, the effect of the niacin and the antipernicious anemia supplement was incomplete. Folic acid was dispensable if the casein level was increased from the original level of 19 per cent in the basal diet to 24 per cent or more. The sparing action of protein on folic acid has been reviewed recently (*Ibid.* **6,** *336* (*1948*)).

Optimum improvement followed the daily administration of 1 U.S.P. unit of the antipernicious anemia fraction, provided that niacin and folic acid were also fed. Higher levels were no more effective and there was no evidence of storage of the active material. Doses smaller than 1 unit were not tried. In one animal, folic acid conjugate was successfully substituted for folic acid. Whether the active substance which completely supplemented niacin and folic acid in these experiments is the antipernicious

anemia factor is not known. Presumably, this question will be answered as soon as adequate supplies of the compound become available (*Nutrition Reviews* **6,** *245* (*1948*)).

Studies of this type bring up many interesting questions. What is the nature of the deficiency syndrome of simple niacin deficiency in dogs? It obviously differs with the complexity of the deficiency and may or may not be identical with the original descriptions of canine pellagra or blacktongue. What is the significance of the combined action of the three compounds, niacin, folic acid, and the active substance in the antipernicious anemia fraction? Do the three act independently or is there a direct relation between them as seems to be indicated in the case of niacin and tryptophan (*Nutrition Reviews* **4,** *182*, *334* (*1946*); **5,** *110*, *163*, *234* (*1947*))? Does either folic acid or the active component in the antipernicious anemia fraction play a role in the niacin-tryptophan picture, and are such effects metabolic or are they the result of reactions proceeding in bacteria in the large intestine (*Ibid.* **6,** *233* (*1948*))? These problems are not limited to the dog. There is abundant evidence that the findings reported by Ruegamer *et al.* will be duplicated, in part at least, in the chick, rat, pig, and monkey, as well as in man (*Ibid.* **2,** *131* (*1944*); **3,** *165* (*1945*); **4,** *11*, *13*, *15*, *91*, *250* (*1946*); **5,** *163* (*1947*); **6,** *307* (*1948*)). It is certain that final solution of these problems will require more exact knowledge of the role played by intestinal microorganisms in producing substances that may exert either a beneficial or a deleterious influence on the nutritional state.

NUTRITION OF CANADIAN SCHOOLCHILDREN

A nutritional study of a group of schoolchildren in Toronto has uncovered a number of interesting facts regarding survey methods and the effectiveness of attempts to improve nutrition.

The preliminary examination of 518 elementary schoolchildren was conducted in the spring of 1946 (R. Crawford, J. Leeson, E. W. McHenry, and W. Mosley, *Canad. Pub. Health J.* **37,** *351* (*1946*)). Both physical examinations and food intake measurements were made. The physical examination was complete and in addition the blood hemoglobin concentration was determined. In other instances, urine analysis was done.

Food intake data were obtained from seven day diet records of 386 children; from the children themselves or from their mothers. Calculations were not made of the quantities of individual nutrients consumed, rather the servings per week of milk, eggs, citrus fruit, other fruit, vegetables, potatoes, meat, liver, bread, cereals, cheese, cakes, and pastry were recorded. The children's likes and dislikes of these foods were also a subject of inquiry. Data were likewise obtained from a visit to the family of each child included in the study.

The nutritional status of the children graded by inspection at the time of the examination showed that 15 per cent were in the excellent, 44 per cent good, 34 per cent fair, and 7 per cent in the poor group. Various physical defects were found in the children, some directly related to nutrition, others not. Thus 35 per cent were underweight, 30 per cent had diseased tonsils, and 12 per cent had hemoglobin concentrations below 12 g. per 100 ml.

With the exception of milk and fruit, the consumption of foods appeared to be adequate, although the intake of vitamin D was not dependable for most of the children (46 of the 518 children were found at the physical examination to have rachitic changes). The authors felt that improvement in nutrition as well as of other health conditions was needed.

During the subsequent two years various "improvement" measures were tried and the

results are presented in the second publication in the series (E. M. Shaver, E. M. Esler, W. Mosley, and E. W. McHenry, *Canad. Pub. Health J.* **39,** *395 (1948)*). Of the 518 children studied originally, 230 were followed for two years (three examinations).

Educational procedures used during the two years were of many kinds, directed both at the parents and at the children themselves. A poster contest to stimulate the intake of vitamin D was effective, but many of the other methods were not. Thus, for example, nutrition classes were poorly attended. Classroom teaching of nutrition was not as effective as hoped because of lack of health training by the teachers.

Improvements, presumably related to the educational program, were almost confined to a decrease in the incidence of diseased tonsils, an improvement in the consumption of fruit and of vitamin D, and an improvement in apparent nutritional status. The latter, as the authors observed, is susceptible to great subjective error. For example, the incidence of rickets, which was 12 per cent in 1946, fell to 6 per cent in 1947, but rose again to 18 per cent in 1948. This apparent rise in the number of rachitic children in 1948 may have been due, at least in part, to the fact that the last physical examination was not conducted by the same physician who conducted the first two examinations.

There was a striking fall in the number of children with low hemoglobin concentrations. Compared to 14 per cent with this "defect," in 1946, the surveys of 1947 and 1948 found an incidence of but 0.5 per cent each. No comment on this dramatic change is made by the authors.

Although the educational program was directed at increasing the consumption of certain foods, subsequent changes in the quantities of these foods eaten, as the authors suggest, might be related to a variety of other circumstances. The availability and price of foods are but two of the many factors to be considered. With respect to milk consumption, at least, only one in 360 mothers gave the considerable rise in cost of milk as a reason for failure to increase consumption. The usual reason given was that the children did not like milk.

In general the educational program was less effective than might have been hoped for. Changing the food habits of a group of individuals is neither easy nor accomplished in a time as short as two years. Best results may be expected if educational efforts are concentrated on very young children when habits are being formed. Furthermore, as the results of these surveys indicate, objective proof of the effect of an educational program is extremely hard to obtain and to assess.

YEAST FOR HUMAN AND LIVESTOCK FEEDING

Growing concern over the world's food problems, and especially in the light of predictions that the world's population will soon exceed its capacity to produce food, is bringing into focus new means of adding to the food supply. Fodder yeast, which has received brief mention in this journal (*Nutrition Reviews* **3,** *286 (1945)*), has been explored extensively as a livestock and human food material in Europe. Particular interest was paid to yeast for feeding purposes in Germany, where it became a diet staple before and during the recent war.

American members of the Allied Intelligence Objective Agency, inspecting German industries after the war, reported that yeast plants in six German cities had capacities in excess of 25,000 tons per year, and that additional plants were under construction at the end of hostilities (J. F. Saeman, E. G. Locke, and G. K. Dickerman, *Paper Trade J.* **123,** *(No. 12), 38 (1946)*). Most of

the sugar for yeast growth was obtained from wood (by acid hydrolysis) or from waste sulfite liquor effluent from pulp mills, to which was added ammonium salts and potassium sulfate. Some newer installations employed a dilute acid hydrolysis of straw, and others utilized the still bottoms obtained from the alcoholic fermentation of wood sugars. The last source was potentially great, for in the usual alcoholic fermentation of wood hydrolysates only hexoses are utilized, and the still bottoms contain large amounts of pentoses, especially xylose and arabinose. For utilization of the pentoses, which also occur in straw, Torula utilis was the organism of choice, although Monilia candida, Candida arborea, and Oidium lactis were also used, as well as mixed Torula strains. No effort was made to maintain pure cultures except with Oidium lactis; at one plant where the food yeast culture was destroyed by the occupying troops, a handful of sweepings from the floor was used to obtain a new inoculum, with reportedly satisfactory results (E. G. Locke, *Pulp and Paper Industry* **20** (*No. 1*), *20* (*1946*)). The latter publication reported further that fodder yeast had found widespread acceptance as a human food throughout Germany and the Scandinavian countries, although it was apparently being used as a supplementary protein in the diet and not as the main source of dietary protein. Twenty grams per day were considered a desirable quantity for human consumption. E. G. Ritzman (*New Hampshire Agr. Exp. Sta. Tech. Bull.* **88** (*1945*)) fed wood yeast to cows without ill effect as judged by levels of blood sugar, uric acid, and cholesterol and the specific gravity of the urine. The digestibility of the dried yeast was reported to be 97.6 per cent, and the metabolizable energy provided was approximately 3 calories per gram of dry yeast. T. F. Macrae, M. M. El-Sadr, and K. C. Sellers (*Biochem. J.* **36,** *460* (*1942*)) found Torula yeast to be beneficial as an addendum to a swine diet containing corn meal and a high-vitamin yeast extract, salts, and cod liver oil. The yeast provided extra growth on this diet to about the same extent as did casein supplements, and no untoward effects from the yeast were noted when it was fed at a 20 per cent level. However, other workers, for example A. C. Thaysen (*Food* **14,** *116* (*1945*)), have indicated that the phosphorus content of yeast is so hgh that extra calcium must be added to diets containing large amounts of the yeast, and that pigs on a high yeast diet develop rickets when kept in the dark. These symptoms did not develop when the animals had access to light. Yeast protein is high in valine and lysine and should therefore be valuable for use in conjunction with cereal diets, although its low methionine content prevents its use in an indiscriminate manner. The bitter taste which is characteristic of brewers' yeast is less pronounced in Torula.

Development of food yeast production in this country has proceeded more slowly, probably due largely to the relatively high cost of yeast protein. W. H. Peterson, J. F. Snell, and W. C. Frazier (*Ind. Eng. Chem.* **37,** *30* (*1945*)), in surveying the economic possibilities of fodder yeast, concluded that the cost of chemicals necessary to produce 1 pound of yeast from wood sugar amounted to about 1 cent. However, addition of production costs raised the estimate to the high level of 25 cents per pound of protein, and it seemed unlikely that it could compete with soybean, fish meal, and other low-cost proteins selling for less than 10 cents per pound, despite its high content of protein, vitamins, and other nutrients.

The desire to secure more efficient utilization of wood waste in the large timber-producing areas has recently stimulated further work with fodder yeast. E. F. Kurth (*Ind. Eng. Chem.* **38,** *204* (*1946*)) and Kurth and V. H. Cheldelin (*Ibid.* **38,** *617* (*1946*)) reported that Torula, Mycotorula, and Hansenula yeasts could adapt to the pentoses in still-bottom waste after repeated transfers in the still-bottom liquor. One hundred

grams of the dried yeast so obtained contained approximately 50 g. of protein, as well as 0.6 mg. of thiamine, 5 mg. of riboflavin, 60 mg. of niacin, 15 mg. of pantothenic acid, 2 mg. of para-aminobenzoic acid, 0.2 mg. of biotin, and 0.3 mg. of folic acid. These values were in good agreement with others previously obtained (*Nutrition Reviews, loc. cit.*). Any appreciable reduction which could be made in sugar content of the effluent from alcohol plants would benefit these plants, and might even make possible their existence; for a single large alcohol-from-wood plant may have as much as one-half million gallons of effluent liquors containing 0.5 to 1.0 per cent sugars, for disposal each day. The biochemical oxygen demand of the still bottoms is reduced by one-half during the growth of the yeast, and it is conceivable that under some conditions fodder yeast might be produced at a financial loss in order that stream pollution might be reduced by the effluent from these alcohol plants.

M. C. Johnson and E. E. Harris (*J. Am. Chem. Soc.* **70,** *2961* (*1948*)) have studied further the acclimatization of various yeasts to wood sugar. They reported that although wood sugar hydrolysates contain many substances which inhibit microbial growth, Torula utilis, as well as nineteen other species and strains of yeast could become acclimatized to wood sugar-mediums after twelve to twenty-seven transfers. E. E. Harris later reported (*see Chem. Eng. News* **26,** *3487* (*1948*)) that over-all yields of yeast from cellulose average 25 per cent, representing a 20 to 25 per cent protein yield calculated on the carbohydrate used. In contrast, feeding of carbohydrate to pigs would result in a protein yield of about 5 per cent. Harris' estimate of yeast production costs was 1.5 cents per pound for the raw materials, preparation, and power costs. This compares with a raw materials cost of 0.5 cents per pound when cannery wastes are employed as the substrate (W. D. Ramage, *Ibid.*).

J. C. Hoogerheide (*see Chem. Eng. News* **26,** *3487* (*1948*)) has pointed out the possibility of employing microorganisms for fat production. Several unnamed strains of yeast were found to be capable of producing up to 60 per cent of their own dry weight as fat, at conversion efficiencies up to 18 per cent of the carbohydrate consumed.

Much progress is being made in debittering of yeast and in otherwise preparing it as an acceptable human food. The work with individual strains appears to have progressed to the extent that specific desired dietary constituents may be produced in preponderant amounts. The authors of the present article, summarizing the results of a recent symposium held in Milwaukee to discuss the use of yeasts in feeding, feel that widespread improvement in the nourishment of the human race may be accomplished through increased attention to large-scale yeast culture.

AVAILABILITY OF NUTRIENTS FROM FLOUR

Wheat is one of the most important crops for both food and feed. In times of shortages man and livestock become keenly competitive for the available supplies of this cereal, and the usual conservation plan includes an increase in the extraction of flour for human consumption, with a resulting decrease in offals for livestock feeding. Obviously, there then occurs a decrease in the production of foods of animal origin. A complete consideration of the nutritional significance of such readjustments must be based upon knowledge of at least the following factors: comparative availability to man of the important nutrients from high and low extraction flour, availability to the animal of the nutrients from wheat offals, efficiency of the animal in the production of

food for human consumption, and the relative importance under the given circumstances for the food supply of the nutrients from cereal versus the nutrients supplied by animal products. New data bearing on any one of these considerations are of interest. The present review discusses some of the studies on the availability to man of nutrients from high and low extraction flours.

Investigations of the availability of nutrients usually consist of determinations of intake and of fecal loss. The difference between the two measures represents "apparent digestibility" and is most often expressed in terms of percentage. It is readily seen that apparent digestibility (= food nutrient − fecal nutrient x 100/food nutrient) is lower than the true digestibility by a quantity equal to the amount of the nutrient added to the feces by the intestinal secretions or by the microorganisms of the gastrointestinal tract. Nevertheless, data on apparent digestibility are of great practical usefulness. Some limitations of interpretation of such data derived from experiments employing distorted dietaries have been noted (*Nutrition Reviews* **1,** *59* (*1942*)).

It is widely agreed that an increase in extraction of flour results in a decrease in the percentage digestibility of calories and nitrogen from wheat. Expressed percentagewise these differences are not particularly striking. Thus, in one investigation (*Report of the Food* (*War*) *Committee of the Royal Society on the Digestibility of Breads* (*March 11, 1918*)) the average percentage utilization of energy for breads made from 80 and 90 per cent extraction flours was 96.14 and 94.50 per cent, respectively. The absolute gain in energy derived from an increase in the extraction of flour from 80 to 90 per cent is much more than this slight loss in apparent available energy. For example, this same report estimates that 100 pounds of wheat yields 122,560 available calories when milled to an 80 per cent flour and 135,500 calories when milled to a 90 per cent meal. The gain in available calories as a result of higher extraction is 13,000.

T. Moran and J. Pace (*Nature* **150,** *224* (*1942*)) have emphasized that the rate of extraction of flour is an unsound basis for comparisons of digestibilities of calories. They state that at a given extraction the digestibility depends upon the composition, conditioning, and method of milling of the wheat. From a consideration of data of other workers, Moran and Pace calculated that the increase of 0.2 per cent in fiber content of a flour decreases the digestibility approximately 1.1 per cent. This prediction is in agreement with more recent studies of R. A. McCance and C. M. Walsham (*Brit. J. Nutrition* **2,** *26* (*1948*)). Wheats of the same extraction may vary appreciably in their fiber contents.

Wheats may vary greatly in protein content. McCance and Walsham (*loc. cit.*) studied a Canadian wheat containing 15.40 g. of protein per 100 g. of wheat and an English wheat with 8.52 g. of protein per 100 g. of wheat. On experimental diets in which bread made from these wheats contributed 87 to 100 per cent of the caloric value, all of the protein was derived from the whole wheat. Under these circumstances the Canadian whole wheat supplied an average of 113 g. of protein and sufficed to maintain 5 of 6 subjects in positive nitrogen balance during the seven day experimental study. Five of 6 subjects were in negative balance while eating the bread made from the English whole grain. The fecal excretion of nitrogen was the same on diets containing the two kinds of wheat—an observation in confirmation of an earlier experience of the same laboratory (R. A. McCance and E. M. Widdowson, *J. Hygiene* **45,** *59* (*1947*)). These observations were interpreted as indicating that the protein of each flour was completely digested and absorbed and that the fecal nitrogen was all metabolic in origin. In the earlier study (McCance and Widdowson, *loc. cit.*) it was noted that the fecal excretion of nitrogen

was correlated with the fiber content of the flour. Thus, it may be concluded that the true digestibility of wheat protein approximates 100 per cent, but that the apparent digestibility of the protein will vary, dependent upon the fiber content of the flour and the protein composition of the wheat.

This apparent decrease in digestibility of wheat protein with higher extraction of flour must be balanced against a difference in biologic value of the protein in higher versus lower extraction flours. Previously reviewed (*Nutrition Reviews* **1,** *131 (1943)*) evidence indicates that this slight difference in digestibility favoring white flour is more than compensated for by the greater biologic value of higher extraction flours. For example, for the rat 10.5 g. of proteins of whole wheat were found equivalent to 13.1 g. of white flour protein.

The apparent digestibility of fat in whole wheat was also studied by McCance and Walsham (*loc. cit.*). They found a mean digestibility of 62.2 and 53.9 per cent respectively for the Canadian and English wheats. It was suggested that this low digestibility of wheat fat may be due to the difficulty with which lipolytic enzymes penetrate the vegetable cells. If such a low figure for the digestibility of wheat fat is accepted, it would mean that a very low conversion factor (approximately 5.5) should be employed in calculating the caloric value of wheat fat.

Calcium balance studies of the subjects on the whole wheat regimens revealed that all were in negative calcium balance throughout the period of whole wheat consumption. Two of the subjects experienced tetany. This effect on calcium metabolism of whole wheat is attributed to the phytic acid in the flour. It is indeed surprising that low calcium tetany could appear in so short a time as twenty days. It would appear desirable to have additional information on these effects of an exclusive whole wheat diet on calcium metabolism.

On the basis of these studies it is not possible to define a food program. It is, however, on such considerations that food policies must be based.

BERIBERI IN BATAAN

Half a century has passed since Eijkmann, Grün, and others demonstrated that beriberi, the scourge of rice-eating mankind in the East Indies and Far East generally, is a dietary deficiency disease. Nearly forty years have passed since interested investigators, notably C. Funk who coined the word "vitamine," demonstrated the preventive and curative action of concentrates prepared from yeast, rice polish, or bran and other foodstuffs. The effective chemical substance, water soluble B or thiamine, has been available as a commercially prepared synthetic product for a decade, largely through the persistent leadership of R. R. Williams. In view of these advances in scientific knowledge, it may appear surprising that frank beriberi remains a medical problem. Its continuance as a hazard to life, unfortunate as it is, has many explanations that involve real economic and human factors, not the least of which is the extraordinary resistance of the individual to alterations in established dietary habits and food practices. Enrichment of staple foods is one method of shortening the time interval between the recognition of the need of a specific chemical in the diet and the assurance that populations have made available and are using suitable natural foodstuffs as sources of the nutrient in question. Such an enrichment program is being initiated in the province of Bataan in the Philippines under the auspices of the Department of Health of the Republic of the Philippines and with the cooperation of the United

States Public Health Service, the Williams-Waterman Fund for the Combat of Dietary Diseases, and Columbia University.

Bataan was selected as the site for the attempt to reduce the incidence of beriberi by the use of enriched rice because of the high mortality from beriberi in the province and because the presence of only one national highway in this area of relatively uniform economic and agricultural conditions makes possible the necessary control of transportation. Before the actual introduction of the enriched rice, a careful survey of beriberi in Bataan was made. The survey included nine of the twelve towns in the province, as well as rural areas, and 12,384 persons out of a total population of 98,457. Some of these base line data for the future assessment of the efficacy of enriched rice in the control of beriberi have been reported (J. Salcedo, E. O. Carrasco, F. R. Jose, and R. C. Valenzuela, *J. Nutrition* **36,** *561 (1948)*).

Beriberi ranks a close second to pulmonary tuberculosis as a cause of death in the Philippines. In 1946 the mortality rates for tuberculosis and beriberi were 170 and 148 per 100,000, respectively. In 1947 the mortality rates for beriberi were 84 in the city of Manila, 132 in all of the Philippines, and 166 in the province of Bataan. The disease is particularly fatal in infants and in 1947 infant deaths constituted over four fifths of the total deaths from beriberi in Bataan. Frank beriberi was found in 1.99 per cent of the population examined, suggestive beriberi in 3.58 per cent, and doubtful or questionable beriberi in 7.24 per cent. Clinical diagnosis of beriberi, including doubtful or suspicious cases, was accepted only when the preliminary conclusion of the survey medical officer was confirmed by physicians in local units of the Bureau of Health. Assuming that the sampling was a fair representation of the Bataan population, nearly 13 per cent showed evidence of a dietary inadequacy of thiamine. With respect to types of subjects examined the order of decreasing incidence was as follows: expectant mothers; nursing mothers; other adults; infants, 0 to 2 years of age; and children, 3 to 15 years of age. Beriberi was as prevalent in rural as in urban areas. In frank beriberi, the most frequent signs in infants were cyanosis and opisthotonos. In children the main symptoms were fatigability, enlarged heart, tingling, numbness, reflex changes, pallor, calf tenderness, and cramps. In adults cyanosis, palpitation, tachycardia, edema, and waist tightness were common in addition to the signs observed in children.

Nine-day dietary histories were obtained from beriberi subjects selected at random in the Bataan area and the ratio of ingested thiamine (in micrograms) to calories was calculated. In 17 cases of frank beriberi, the ratio was less than 0.30 in 15, less than 0.25 in 13, and less than 0.20 in 8. Out of 122 subjects classified as showing clinical evidence of frank, suggestive, or doubtful beriberi the ratio was less than 0.30 in 86 per cent, less than 0.25 in 69 per cent, and less than 0.20 in 34 per cent. A value under 0.25 is indicative of clinical beriberi according to R. R. Williams and T. D. Spies ("Vitamin B_1 (Thiamine) and its Use in Medicine," *p. 95, MacMillan Co., New York (1938)*). The thiamine-calory ratio was also determined in over 60 "normal" subjects in order to have a control group for comparison of fasting thiamine excretions. The complete data for this group are not given in the report of Salcedo *et al.*, but the fact that several of the subjects were eliminated as normals because their ratio values were less than 0.25 suggests that the intake of thiamine was generally low.

The urinary output of thiamine during the thirteenth postabsorptive hour was determined in beriberi patients in 1547 instances. The results varied from 0 to 8.5 micrograms per hour with a mean value of 2.7. The excretion was approximately the same regardless of classification of the severity of beriberi as frank, suggestive, or doubtful so that this test appeared to have limited usefulness as a diagnostic tool. In

was correlated with the fiber content of the flour. Thus, it may be concluded that the true digestibility of wheat protein approximates 100 per cent, but that the apparent digestibility of the protein will vary, dependent upon the fiber content of the flour and the protein composition of the wheat.

This apparent decrease in digestibility of wheat protein with higher extraction of flour must be balanced against a difference in biologic value of the protein in higher versus lower extraction flours. Previously reviewed (*Nutrition Reviews* **1,** *131 (1943)*) evidence indicates that this slight difference in digestibility favoring white flour is more than compensated for by the greater biologic value of higher extraction flours. For example, for the rat 10.5 g. of proteins of whole wheat were found equivalent to 13.1 g. of white flour protein.

The apparent digestibility of fat in whole wheat was also studied by McCance and Walsham (*loc. cit.*). They found a mean digestibility of 62.2 and 53.9 per cent respectively for the Canadian and English wheats. It was suggested that this low digestibility of wheat fat may be due to the difficulty with which lipolytic enzymes penetrate the vegetable cells. If such a low figure for the digestibility of wheat fat is accepted, it would mean that a very low conversion factor (approximately 5.5) should be employed in calculating the caloric value of wheat fat.

Calcium balance studies of the subjects on the whole wheat regimens revealed that all were in negative calcium balance throughout the period of whole wheat consumption. Two of the subjects experienced tetany. This effect on calcium metabolism of whole wheat is attributed to the phytic acid in the flour. It is indeed surprising that low calcium tetany could appear in so short a time as twenty days. It would appear desirable to have additional information on these effects of an exclusive whole wheat diet on calcium metabolism.

On the basis of these studies it is not possible to define a food program. It is, however, on such considerations that food policies must be based.

BERIBERI IN BATAAN

Half a century has passed since Eijkmann, Grün, and others demonstrated that beriberi, the scourge of rice-eating mankind in the East Indies and Far East generally, is a dietary deficiency disease. Nearly forty years have passed since interested investigators, notably C. Funk who coined the word "vitamine," demonstrated the preventive and curative action of concentrates prepared from yeast, rice polish, or bran and other foodstuffs. The effective chemical substance, water soluble B or thiamine, has been available as a commercially prepared synthetic product for a decade, largely through the persistent leadership of R. R. Williams. In view of these advances in scientific knowledge, it may appear surprising that frank beriberi remains a medical problem. Its continuance as a hazard to life, unfortunate as it is, has many explanations that involve real economic and human factors, not the least of which is the extraordinary resistance of the individual to alterations in established dietary habits and food practices. Enrichment of staple foods is one method of shortening the time interval between the recognition of the need of a specific chemical in the diet and the assurance that populations have made available and are using suitable natural foodstuffs as sources of the nutrient in question. Such an enrichment program is being initiated in the province of Bataan in the Philippines under the auspices of the Department of Health of the Republic of the Philippines and with the cooperation of the United

States Public Health Service, the Williams-Waterman Fund for the Combat of Dietary Diseases, and Columbia University.

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50 apparently "normal" subjects with thiamine-calory ratios above 0.25, the fasting one-hour excretion of thiamine averaged 6.1 ± 3.4 micrograms. This value is low compared with the average of 11 micrograms reported for 46 normal subjects in the United States (R. E. Johnson, C. Henderson, P. F. Robinson, and F. C. Consolazio, *J. Nutrition* **30,** *89 (1945)*).

The attempt to eradicate beriberi by a food enrichment program will be followed with interest. It is reasonable to expect that considerable improvement of general health will result because eating rice is almost universal in Bataan. The report does not indicate average amounts consumed but it is pointed out that in two thirds of the families surveyed meat was eaten only once a week, and in one half of the families, vegetables were eaten not more than twice a week. Ninety per cent of the families consumed fish six or seven times a week. It is noteworthy that it has been a common practice in Bataan to wash rice two to four times before cooking and that all washings were discarded by 81 per cent of the subjects. It is to be hoped that future surveys in the Bataan area will indicate whether a decrease in the incidence of beriberi is correlated with the simple substitution of enriched for unenriched rice in otherwise unaltered dietaries or whether it is correlated with eating enriched rice together with a wider variety of foodstuffs. Such data may throw light on the question of the role of other factors in the etiology of endemic beriberi in large populations.

PROTEINS OF BLOOD PLASMA AND SERUM IN NORMAL AND RHEUMATIC CHILDREN

Protein patterns as determined by electrophoresis have been found in the serums of normal adults. Few studies have been made in children, although a high gamma-globulin has been reported in newborn infants, correlating with the natural immunity in this age group (L. G. Longsworth, R. M. Curtis, and R. H. Pembroke, *J. Clin. Invest.* **24,** *46 (1945)*). The percentage of albumin is higher in young children and decreases with age. Marked changes in electrophoretic pattern have been observed in disease. Decreased albumin levels have been noted in malnutrition, kidney disease, and whenever globulin values are elevated in serums of normal total protein content. An increase in alpha-globulin is associated with inflammatory reactions while a rise in beta-globulin appears to be associated with liver damage. Elevation of gamma-globulin occurs during or following infectious diseases.

In the description of the normal electrophoretic pattern, the relation of antecedent illness has not been considered nor has the possible influence of genetic differences been explored. R. Lubschez (*Pediatrics* **2,** *570 (1948)*) has studied normal children in apparent health to determine the possible influences of heredity, age, sex, and antecedent illness on electrophoretic pattern. Total serum protein levels were within normal limits in all the children studied. In 30 children, aged 2 to 11 years, with no record of illness for four months, mean values for the relative concentration of various protein components were in close agreement with those obtained by V. P. Dole (*J. Clin. Invest.* **23,** *708 (1944)*) in 15 healthy young adult males, except for greater variation in the albumin and gamma-globulin peaks. No significant difference was observed between boys and girls. The albumin level was slightly higher and the gamma-globulin slightly lower in young children (aged 2 to 4 years). The small increase in gamma-globulin level with increasing age may reflect the gradual production of antibodies. Two determinations made on infants under 1 year of age fell within the normal limits found in the study.

The electrophoretic pattern of 27 children in apparent health, but who had experienced some type of infection within four months, showed differences from the previous series in all of the protein components except beta-globulin. The other globulin levels increased and the albumin level decreased by about one standard deviation. Several abnormal values (more than twice the standard deviation) were observed for each component except beta-globulin. An elevation of gamma-globulin was noted in 44 per cent of the determinations. Illness within previous months produced the greatest number of variations, but abnormalities were still noted two or three months after infection. There was some correlation between pattern abnormalities and the duration and severity of illness. Seven children susceptible to rheumatic fever on a genetic basis exhibited no specific differences in electrophoretic pattern.

M. G. Wilson and R. Lubschez (*Pediatrics* **2,** *577 (1948)*) obtained blood specimens for electrophoretic analysis from 42 rheumatic children during periods of apparent health, following respiratory illness, and during rheumatic fever. They found an elevation in the gamma-globulin component, lasting weeks to months, following an antecedent respiratory illness with or without the development of fever. During acute rheumatic fever, the gamma-globulin component was normal in the absence of antecedent illness. It appears therefore that the elevation of the gamma-globulin fraction is not a function of the rheumatic process but is a reflection of previous infection. The alpha-globulin components were usually elevated during febrile periods. No evidence was obtained "that the immune response of rheumatic subjects to infections, presumably streptococcal in origin, differed from that of non-rheumatic individuals."

E. L. Knapp, J. W. Giffee, and R. L. Jackson (*J. Lab. Clin. Med.* **33,** *1490 (1948)*) have found the changes in electrophoretic pattern during the active phase of rheumatic fever to be a consistent and marked decrease in values for albumin with an increase in values for gamma-globulin, alpha$_2$-globulin, and fibrinogen. As the clinical condition of the child improved, the distribution of plasma proteins shifted toward normal. The sedimentation rate and plasma albumin generally returned to normal simultaneously. These workers also reported a low recurrence rate of a highly susceptible group of rheumatic children who received special attention to improve their diets and home care. The diets of these children had previously been deficient in protein.

B. F. Chow (*J. Clin. Invest.* **26,** *883 (1947)*) concluded from a series of one hundred and ninety-eight determinations in patients with several diseases, that lowered albumin and elevated alpha-globulin levels were a reflection of some fundamental mechanism and not characteristic of specific disease. An increase in one or both alpha components is often observed in febrile states and following severe trauma (A. Chanutin and E. C. Gjessing, *J. Biol. Chem.* **165,** *421 (1946)*). Elevation of plasma lipids has been shown to effect the electrophoretic pattern, large beta-globulin peaks and an increase in gamma-globulin being regularly observed (*Nutrition Reviews* **4,** *144 (1946)*). Further investigation of this nature may yield information of fundamental importance concerning relations between serum proteins and immune mechanisms.

DIETARY NEEDS OF MAN FOR PYRIDOXINE

Several more vitamins are recognized as dietary essentials for laboratory animals than are listed as requirements for man. Many of the apparent differences are undoubtedly due to the practical difficulty of feeding highly purified diets to man and thereby revealing dietary deficiences. Some species differences must be due to

differences in the ability of the tissues to synthesize the vitamin, as in the case of ascorbic acid, while other variations may depend on differences in intestinal flora and synthesis. Certainly with the increasing recognition of the role of vitamins in fundamental metabolic processes there is reason to believe that the actual tissue requirements of vitamins in various mammalian species are similar, whatever may be the source of the particular vitamin. This fully justifies extensive dietary experiments with animals as a direct approach to the problems of nutrition, health, and disease in man. Dietary constituents recognized as essential for man are listed as such because fairly large segments of the population show easily recognizable symptoms of deficiency due to unique food habits or shortages. Individual food habits or idiosyncrasies, gastrointestinal abnormalities or disease, and other conditions may, however, result in conditions in man which are due to, but not yet recognized as nutritional deficiencies. Hence more experiments must be conducted directly with man to reveal the significance to him of the many factors now recognized only by animal experimentation.

Pyridoxine is one of the vitamins known to be essential in the diet of several species, but it has not been demonstrated as essential in the diet of man. It is widely distributed however in the usual food items consumed by man. There have been therapeutic claims for pyridoxine in various disease conditions, but it is not clear that any effects were due to a correction of pyridoxine deficiency. Pyridoxine is known to be a part of the enzyme system involved in the fundamental metabolic reaction of transamination.

The study of W. W. Hawkins and J. Barsky (*Science* **108**, *284* (*1948*)) attempting to produce pyridoxine deficiency in man is therefore of interest. One male subject was placed on a purified diet containing sucrose, corn oil, vitamin-free casein, mineral salts, and cod liver oil concentrate, with supplements of thiamine, calcium pantothenate, niacin, riboflavin, ascorbic acid, choline, inositol, and an extract of rice polish concentrate from which pyridoxine had been removed. This unpalatable diet was consumed at levels to supply some 2200 calories per day and continued for a period of fifty-four days. At the end of this period the same diet was supplemented with 10 mg. of pyridoxine per day for a week. During the pyridoxine deprivation period there were no changes in nitrogen balance, blood nonprotein nitrogen, blood pressure, or hemoglobin which could be definitely attributed to the lack of pyridoxine. The investigators state that the subject was aware of considerable mental confusion and depression, but apparently this was only subjective.

There was a possible change in the blood white cell picture. Just a few days before pyridoxine was given there seemed to be a sharp rise in the total white cell count and percentage of lymphocytes, and a decrease in neutrophils. Immediately after adding pyridoxine to the diet, a reversal of these changes occurred. Unfortunately the observations were too few to be certain of these changes. Although white cell changes have been recorded in pyridoxine deficiency in monkeys and after administration of large amounts of this vitamin to man, the investigators feel that the changes they observed could not be unequivocally considered due to a pyridoxine deficiency.

The authors point out that it requires months to produce pyridoxine deficiency in monkeys and that this vitamin may be supplied in considerable amounts by intestinal bacteria. Thus there are still too few accurate descriptions of vitamin deficiencies in man, and despite the attempt described, the signs of pyridoxine deficiency in man are not yet known.

NOTES

Letter to the Editor

Dear Sir:

In the November 1948 issue of *Nutrition Reviews*, there was a report entitled "The hyperglycemic effect of thiourea and related compounds."

In 1946, I published an experimental work on "Effect of the thiouracil on alloxan and pancreoprive diabetes" (J. L. R. Candela, A. Gascon, and J. A. Paniagua, *Medicina (Madrid)* **14,** *312 (1946)*). Its results can be summarized as follows:

(1) In the great majority of diabetic animals (dogs) there is an increase of glycemia, which lasts for about ten days, when thiouracil is given (1 cg. per Kg. weight).

(2) When the hyperglycemic effect of thiouracil on alloxan and pancreoprive diabetes disappears, there is an increased carbohydrate tolerance, shown by a decreased glycemia.

(3) The hyperglycemic effect was then considered as due to the hypofisis. We supposed the decreased glycemia to be due not to a thyroid effect, but to a tissue action.

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An Amino Analogue of Pantothenic Acid

The ethyl ester of a new analogue of pantothenic acid has been prepared in which the hydroxy group alpha to the carboxyl of the pantoic acid residue has been replaced by an amino group (F. W. Holly, R. A. Barnes, F. R. Koniuszy, and K. Folkers, *J. Am. Chem. Soc.* **70,** *3088 (1948)*). This compound, ethyl DL-beta'-(alpha-amino-beta, beta - dimethyl - gamma - hydroxybutyryl-amino)-propionate, which might for convenience be called amino pantothenic acid, possesses growth-promoting properties that are unusual among vitamin analogues.

Amino pantothenic acid, when furnished to rats on a pantothenic acid-free diet, had no growth-promoting ability. When Lactobacillus arabinosus was employed as the test organism, the amino compound was less than 0.7 per cent as active as the vitamin. Moreover, the new analogue did not inhibit growth of either species; it did not antagonize pantothenic acid in L. arabinosus when added at ten times the weight of the vitamin which produced maximum cell growth. However, when sufficient pantothenic acid to yield half-maximum growth was added with an equal quantity of the analogue (0.02 microgram of each), maximum growth of the microorganism resulted.

Although the data presented were not extensive enough to permit lengthy speculation on the reason for the ability of the analogue to function in a vitamin-like manner in the presence of the vitamin, it seems possible that adaptation of the organism may have taken place. This is not common among the lactic bacteria, although L. D. Wright and H. R. Skeggs (*J. Biol. Chem.* **159,** *611 (1945)*) have demonstrated adaptation of L. arabinosus to the synthesis of tryptophan, and V. H. Cheldelin, M. J. Bennett, and H. A. Kornberg (*Ibid.* **166,** *779 (1946)*) observed adaptation to thiamine synthesis by Lactobacillus fermenti. However, both of these developments were accomplished only after several transfers, and both syntheses were probably from fragmentary precursors. The present phenomenon seems more nearly analogous to the reported superior activity of D-glutamic acid for L. arabinosus and Lactobacillus casei in the presence of the naturally occurring L-isomer (L. R. Hac, E. E. Snell, and R. J. Williams, *Ibid.* **159,** *273 (1945)*).

Further work appears necessary to determine the mechanism by which amino pantothenic acid is converted into a vitamin-active material. However, regardless of the

mechanism, the possibility arises that the amino compound may exist in nature, and could affect microbiologic pantothenic acid assays. The corresponding amino analogue of pantoic acid, which has been called pantonine, is believed by W. W. Ackermann and H. Kirby (*J. Biol. Chem.* **175,** *483 (1948)*), on the basis of paper chromatography separations, to occur naturally. If this is true, it seems reasonable to suppose that amino pantothenic acid might also occur naturally.

Amino and Amino Acid Conjugates of Pyridoxine

Several papers during recent months have been devoted to the preparation and study of analogues of pyridoxine in which pyridoxal is conjugated with amines or amino acids. The purpose of the work, as outlined by E. E. Snell and J. C. Rabinowitz (*J. Am. Chem. Soc.* **70,** *3432 (1948)*), was to explore the hypothesis that transamination reactions, several of which are known to be mediated by pyridoxine-containing systems, might occur through the actual combination of the vitamin (pyridoxal) with the amino group of an amino acid. The product, an unsaturated Schiff base type of compound, might then undergo a shift of the double bond, and upon hydrolysis the amino and keto groups of the original pair would be transferred. With this in mind, D. Heyl, S. A. Harris, and K. Folkers (*Ibid.* **70,** *3429 (1948)*) prepared Schiff base conjugates of pyridoxal with twenty common amino acids. Also, since it was considered possible that the Schiff bases might be hydrogenated prior to decomposition in the cell, the Schiff bases prepared were hydrogenated to the corresponding pyridoxylamino acids. The compounds of both series were tested for both vitamin and antivitamin activity in microorganisms, and the pyridoxylamino acids were tested for vitamin activity in rats.

The results of testing however did not support the above supposition, for the compounds were not active *per se*. The Schiff bases were approximately as active as pyridoxal, but this was apparently due to spontaneous hydrolysis, since the yellow color disappeared gradually in water solution. The pyridoxylamino acids, on the other hand, possessed only slight activity (less than 0.1 per cent to 1.0 per cent of the activity of pyridoxal) when added to an unheated, air-free medium. When air was present and the medium was sterilized by autoclaving, activities frequently approached that of pyridoxal. That the increase in activity was due to oxidative degradation was strongly indicated by the fact that antioxidants such as cysteine or ascorbic acid prevented this increase.

Condensation of pyridoxal with several amines, including tyramine, tryptamine, histamine, and others, followed by hydrogenation to the pyridoxyl derivatives, yielded compounds which were nearly as active as pyridoxine in rats (D. Heyl, E. Luz, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.* **70,** *3669 (1948)*). It seems likely that degradation to the original compounds also took place with these conjugates.

It is evident that further studies will be necessary to discover the mechanism by which pyridoxal participates in transamination. The present experiments do not invalidate the authors' ideas, however, since it is possible that condensations should be made through pyridoxal phosphate (the structure of which is still unknown) rather than pyridoxal, or that pyridoxal or the coenzyme must first be joined to the enzyme protein before condensation can take place.

Recent Nutrition Book

Investigations of Human Requirements for B-Complex Vitamins. Bulletin of the National Research Council, No. 116, June 1948. Published by the National Research Council, National Academy of Sciences, Washington, D. C. Price: $1.00.

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mechanism, the possibility arises that the amino compound may exist in nature, and could affect microbiologic pantothenic acid assays. The corresponding amino analogue of pantoic acid, which has been called pantonine, is believed by W. W. Ackermann and H. Kirby (*J. Biol. Chem.* **175,** *483 (1948)*), on the basis of paper chromatography separations, to occur naturally. If this is true, it seems reasonable to suppose that amino pantothenic acid might also occur naturally.

Amino and Amino Acid Conjugates of Pyridoxine

Several papers during recent months have been devoted to the preparation and study of analogues of pyridoxine in which pyridoxal is conjugated with amines or amino acids. The purpose of the work, as outlined by E. E. Snell and J. C. Rabinowitz (*J. Am. Chem. Soc.* **70,** *3432 (1948)*), was to explore the hypothesis that transamination reactions, several of which are known to be mediated by pyridoxine-containing systems, might occur through the actual combination of the vitamin (pyridoxal) with the amino group of an amino acid. The product, an unsaturated Schiff base type of compound, might then undergo a shift of the double bond, and upon hydrolysis the amino and keto groups of the original pair would be transferred. With this in mind, D. Heyl, S. A. Harris, and K. Folkers (*Ibid.* **70,** *3429 (1948)*) prepared Schiff base conjugates of pyridoxal with twenty common amino acids. Also, since it was considered possible that the Schiff bases might be hydrogenated prior to decomposition in the cell, the Schiff bases prepared were hydrogenated to the corresponding pyridoxylamino acids. The compounds of both series were tested for both vitamin and antivitamin activity in microorganisms, and the pyridoxylamino acids were tested for vitamin activity in rats.

The results of testing however did not support the above supposition, for the compounds were not active *per se*. The Schiff bases were approximately as active as pyridoxal, but this was apparently due to spontaneous hydrolysis, since the yellow color disappeared gradually in water solution. The pyridoxylamino acids, on the other hand, possessed only slight activity (less than 0.1 per cent to 1.0 per cent of the activity of pyridoxal) when added to an unheated, air-free medium. When air was present and the medium was sterilized by autoclaving, activities frequently approached that of pyridoxal. That the increase in activity was due to oxidative degradation was strongly indicated by the fact that antioxidants such as cysteine or ascorbic acid prevented this increase.

Condensation of pyridoxal with several amines, including tyramine, tryptamine, histamine, and others, followed by hydrogenation to the pyridoxyl derivatives, yielded compounds which were nearly as active as pyridoxine in rats (D. Heyl, E. Luz, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.* **70,** *3669 (1948)*). It seems likely that degradation to the original compounds also took place with these conjugates.

It is evident that further studies will be necessary to discover the mechanism by which pyridoxal participates in transamination. The present experiments do not invalidate the authors' ideas, however, since it is possible that condensations should be made through pyridoxal phosphate (the structure of which is still unknown) rather than pyridoxal, or that pyridoxal or the coenzyme must first be joined to the enzyme protein before condensation can take place.

Recent Nutrition Book

Investigations of Human Requirements for B-Complex Vitamins. Bulletin of the National Research Council, No. 116, June 1948. Published by the National Research Council, National Academy of Sciences, Washington, D. C. Price: $1.00.

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